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**BCG-VACCINATION
TUBERCULIN ALLERGY AND TUBERCULOSIS
IN SCHOOL CHILDREN**

A Follow-up Study from Stockholm's Elementary Schools,
1945-51, with Special Regard to Social Factors

By

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Translated from the Swedish

by

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Preface

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Herbert Enell

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Introduction

A. General Considerations

Judgement of BCG-vaccination and the follow-up investigation of BCG-vaccinated material creates distinct difficulties on account of the special nature of the vaccination and the major unsolved problems which still exist concerning the nature of tuberculin allergy and also regarding the closer character of natural and acquired immunity against tuberculosis. *Irvine's* words (1949) can express the situation: "Though at first sight such an experiment would appear to be a simple procedure, the large number of variables that affect the susceptibility to tuberculosis infection of any individual make it almost impossible to design an experiment that is statistically watertight."

No author has yet published a series with a control material comparable and quite free from objection—even if a few have come very near to this. Articles which have demonstrated a good effect of BCG-vaccination have—on account of the above-mentioned factors—had difficulty in getting generally accepted in spite of their being carried out with the greatest possible degree of precision. It is, therefore, my opinion that even for a long time in the future different BCG-vaccination series ought to be evaluated very critically and from every aspect that can be thought of. This is the only way to throw further light on the possible value of BCG-vaccination.

In the Spring of 1950 it was clear that the children—who since the Spring term of 1945 had undergone voluntary BCG-vaccination in the junior forms of Stockholm's "folkskolor" (Council or Elementary schools)—should be a suitable material for the investigation of some of these unsolved problems. From the beginning I was well aware that the control material would not be quite representative. A large percentage agreed to the voluntary vaccination and the control material therefore only consisted of those children who did not have the opportunity for it, or where vaccination was refused. But owing to the willing attitude to BCG-vaccination that generally exists in Sweden it was not possible to withdraw the

right to be vaccinated from a sufficiently large portion of school children to enable a control that was statistically free from criticism to be carried out.

After six years of BCG-vaccination of the school children of Stockholm there were many instances when it was important to have further information about it. *The Social Authorities*, who paid the heavy costs which the Vaccination Organisation incurred, asked themselves: Does this pay, or is the money better spent on other tuberculosis prophylactic measures? *The parents* often asked the doctors: How long is a child protected following a successful BCG-vaccination? How often is re-vaccination necessary? Possibly some parents have even asked: Do the advantages outweigh the discomforts of BCG-vaccination (i.e. the tuberculin test, needle, local and general reaction, etc.)? Finally, *pediatricians, tuberculosis research worker and other scientists*, in addition to the above-mentioned questions, asked: What part does human super-infection play in the maintenance of a post-vaccinal tuberculin positivity? How big a rôle do the social factors play in comparison with BCG-vaccination in the fight against tuberculosis? The object of the following work is in some way to give an answer to these questions.

B. Swedish School Organisation

The Swedish school organisation for the period of the investigation (1945—51) was briefly as follows: School is compulsory when the children become 7, and only exceptionally do they begin school earlier. The majority of children in Stockholm (95 per cent) attend so-called "folkskolor" (Elementary schools) during their first four years at school and only about 5 per cent go to private schools. At the age of 10—11 a portion of the Elementary school children from form IV changes over to the "läroverk" or "mellanskolor" (Types of Secondary schools). The period of study at the "läroverk" is eight years, terminating in the "studentexamen", and only after passing this examination are they eligible to enter a University. There are different kinds of "mellanskolor", some partly specialised, technical, commercial or the like, and pupils get five years tuition there. The compulsory period of attendance in Elementary schools for those who do not enter the higher schools is up to the age of 15, i.e. to the form VIII. One can reckon that about a quarter of all children are educated in Elementary schools up to this form (See diag. page 23).

C. The Planning of the Author's Investigation

When this investigation was planned in the Spring of 1950 it could be seen that for practical reasons it could not include the whole of Stockholm's school children, but only a mere portion. It was thus important to select the material in such a way that it was representative of a cross-section of Stockholm's Elementary school population, above all taking into consideration social classes and the standard of the homes. It was essential that those in a better social position should not be over-represented. Besides, such schools ought to be chosen where in earlier years tuberculin tests had been carried out as thoroughly as possible and BCG-vaccination was the routine. This investigation was eventually carried out at seven schools in Stockholm, having a total of 4,105 pupils in the forms concerned. The motives for the choice of these schools are given more fully in an account of the material in Ch. IV.

D. Definitions and Abbreviations

Dispensär	a Swedish <i>organisation</i> for the prophylaxis and control of tuberculosis. This organisation has Central and District Dispensaries (i.e. <i>Clinics</i> + an extensive record system): the former are usually connected with sanatoria or hospitals. District Dispensaries are "free" from these connections, and are run by "Provincial doctors" (who are part "G.P." and part "M.O.H.").
E.N.	Erythema nodosum.
Immunity	the acquired specific resistance produced by the first infection. See page 13.
Inversion, inverters	the change from a negative to positive tuberculin reaction in BCG-vaccinated or non-vaccinated individuals.
M-	positive Mantoux 100 TU, but negative Patch test.
Mx. (or M)	Mantoux intracutaneous Tuberculin test.
Natural resistance	the inherent unspecific power to resist tuberculous infection in general. See page 12.
Neo-T	Neo-Tuberculin test: Percutaneous tuberculin ointment test without plaster.
P	Patch tuberculin test (Modif. Moro).
P-	positive Patch (Plaster) tuberculin test.

Re-infection	= a new external infection on a person in whom the previous infection is completely healed.
Reversion, reverters	= the change from a positive to negative tuberculin reaction in BCG-vaccinated or spontaneously positive individuals.
SBL	= Statens Bakteriologiska Laboratorium, Stockholm, Sweden.
Superinfection	= a new external infection superimposed on a person in whom the previous infection (or BCG-vaccination) is still active. See page 20.
Tb.	tuberculosis.
TU	= 1 Tuberculin Unit (TU) is equal to 0.01 mg International Standard Tuberculin (O.T.) or 0.00002 mg International Standard Reference Preparation of Purified Protein Derivative (P.P.D.) (WHO Sub-Committee on Biological Standardisation).
Tuberculin allergy	= a hypersensitivity to the antigenic portions of the tubercle bacillus—as a rule caused by living tubercle bacilli existing in the organism.
+ ve	= positive.
- ve	= negative.

CHAPTER I

Short Historical Notes and Earlier Investigations

A. Preventive Immunisation against Tuberculosis

a. *Vaccination with killed bacilli*

Since Koch's discovery in 1882 of the tubercle bacillus and in 1890, tuberculin, trials were first made with tuberculin in the treatment of and prophylaxis against tuberculosis. These trials failed completely.

Vaccines containing killed bacilli were used early, but the initial results were discouraging. This procedure is still used with a varying degree of success. Of these vaccines, the one most in use at present is probably "Anatuberculin Petragnani" (V.P.S.) developed by Salvioli. The bacilli are fixed with formaldehyde and the vaccine is given subcutaneously, especially to newborn infants (Salvioli 1951, Rondinini & Lenzi 1951). Another vaccine, the so-called AO-vaccine (Arima, Aoyama & Ohnawa 1937), consists of bacilli treated with saponins. Heat-killed virulent human bacilli have also been used (Goodwin & Schwentker 1934, Opie, Flahiff & Smith 1939), and also bacilli killed through exposure to ultra-violet rays (Smithburn & Lavin 1939, Olson, Habel & Piggott 1947).

b. *Vaccination with living bacilli*

Early attempts in the treatment of human tuberculosis were made with fully virulent bacilli (Webb & Williams 1911, Selter 1925, Möller 1926) but without great success. Most investigators worked with strains which, through various procedures, had been attenuated, and papers dealing with this subject are numerous. They have been extensively reported by Irvine (1949). Special mention may be made of von Behring's "bovovaccine" 1902, which was used on cows. It was soon found, that though animals treated with this and other similar vaccines showed an increased resistance to infection, they also excreted bacilli (Griffith 1913, Heimbeck 1927).

In 1908 Calmette and Guérin began cultivating Nocard's bovine tubercle strain to lessen its virulence, and were able—in animal ex-

periments—to follow how the strain lost its virulence with time (Calmette 1924, 1928) until in 1924 *Calmette* thought himself justified in declaring this strain as "virus fixe". BCG (Bacillus-Calmette-Guérin) was first used in 1921 by *Weill-Hallé* on infants, without apparent harm. At this stage the vaccine was only given orally. The reason why they concentrated on babies was that they wished to give the earliest possible protection and anticipate "the natural infection"—especially as they were fully aware of the severity of infant tuberculosis. After a few years several workers (*Weill-Hallé & Turpin* 1925, *Heimbeck* 1927 etc.) started giving the vaccines subcutaneously and shortly afterwards in 1927, intracutaneously (*Wallgren* 1928, *Keresztsuri, Park & Schick* 1932). Several percutaneous methods have eventually been suggested (*Rosenthal* 1939, modif. *Négre & Bretey* 1939, *Weill-Hallé* 1939, *Birkhaug* 1944). The intracutaneous route of administration as described by *Wallgren* is the one most used to-day in Europe and has also been practised in the International Tuberculosis Campaign of the UNICEF (United Nations International Children's Emergency Fund) in which more than 17,000,000 people have been inoculated with BCG.

In Latin-America the original oral route of vaccination has been retained, which has been modified principally by *de Assis* (1950). Because of local conditions it is thought to be the most advantageous there—even though there are seldom more than 50 per cent inverters (*Irvine* 1949). The vaccine is generally given to newborn infants and consecutive doses are given monthly for the first 6 months. This method, and its results have been reported by *Sayé* (1940), *Feldman* (1949), *Rosenberg* (1951), *Martins & Sampaio* (1953) etc.

In England, where BCG-vaccination has been used to a remarkably small extent, the "Vole-bacillus", described by *Wells* in 1937, has gained certain ground. The virulence of this strain is said to be about the same as that of BCG.

For further details concerning the history of BCG-vaccination and earlier experiments with this strain, the reader is referred to *Calmette* (1928), and *Irvine* (1949) among others.

B. BCG-Vaccination in Sweden

After *Heimbeck* (1927) in the mid-twenties had shown that especially tuberculin negative individuals are in need of protection (because they have a higher tuberculosis morbidity) *Wallgren* in 1927 started vaccinating

ing tuberculin negative children from tuberculous environments in Gothenburg. He soon found that the intradermal method in comparison with subcutaneous injection offered a more prolonged post-vaccinal tuberculin sensitivity and yet had far less local complications than had previous routes. This method quickly gained ground in Sweden, but during the first decade it was principally used on individuals who were threatened by tuberculosis through family or occupational contacts.

During the 1930's BCG-vaccination fell into disrepute as a result of its unrestrained and unscientific use on the continent, and even more so after the Lübeck disaster of 1930 (Nielsen 1953), in which 72 children were killed by oral BCG-vaccine which had been contaminated with highly virulent human tubercle bacilli. Widespread adoption of the BCG-method was delayed until the following decade, when, in co-operation with Svenska Nationalföreningen mot Tuberkulos (The Swedish National Association against Tuberculosis), BCG-vaccination was eventually used for persons not actually threatened by tuberculosis. Mass-vaccination of conscripts, day-nursery children, and school children was successively introduced. *Törnell* was the pioneer in the latter field, and in 1941 *Wallgren* stressed that a systematic BCG-vaccination of tuberculin negative school children is "an extremely rational prophylactic measure". From 1942-1943 on these measures were rapidly introduced all over Sweden and, in addition to this, in 1944-1945 inoculation of newborn infants in the maternity wards was introduced. Further data concerning these activities will be presented in Chapters II and VIII. It is estimated that of Sweden's total population of over 7,000,000 people close on 1,500,000 have been inoculated (Lundquist 1954).

C. Previous Investigations

a. General survey

For reviews of the literature the reader is referred to works by *Aronson* (1948), *Daelen* (1950), *Nielsen* (1953), who have made extensive contributions. *Nielsen* gives a detailed account of the bacteriological and animal experimental work which has been done to study the varying virulence of the BCG-strain (unfortunately only published in Danish).

A considerable number of scientific reports dealing with the effectiveness of the BCG-vaccination have been published. More or less valid objections may be raised against all of them, and critical analyses have been made by *Levine* (1947), *Wilson* (1947), *Wallygren* (1948) among

others. The most serious objection to most papers is the lack of a wholly acceptable control group, a vital question which will be referred to later on. The most convincing materials so far have been published by Aronsen (1946, 1948, 1952) and by Hyge (1947, 1949). The controls of the latter did not, however, consist of alternate cases. All reports concerning the value of BCG-vaccination, and which have been at least fairly adequately controlled have demonstrated protection through this method, with the exception of Levine and Sackett (1946). As Irvine (1949) remarks, "even reports without such watertight controls are of value".—"The presumptive evidence that has been collected in this manner is so great and the results so impressive" that referring to these "is essential in weighing up the evidence". All these earlier works have been extensively reviewed by previous authors in this field. Irvine (1949) has already been mentioned, but I refer also to Rinvik (1944), Törnell (1947), Hertzberg (1948), Breu (1950), Dahlström and Difs (1951), Aronson et al (1952), Dahlström (1953), Daelen (1953), Kleinschmidt (1953), Nielsen (1953). Further reference will be made in text and tables to various authors and the problems with which they have dealt.

There are two matters which have particular bearing on the central problems of this treatise: these are duration of the tuberculin sensitivity after BCG-vaccination and the resistance produced in man after BCG. This would justify a more detailed account of the results and conclusions of earlier workers. About other topics on which I present results in this treatise, so little is written that I have found it better to mention them in connection with my own findings.

b. Immunity to and resistance against tuberculosis

A fundamental question in the scientific evaluation of the relative immunity against tuberculosis which may be demonstrated in humans is the relation immunity against tuberculosis to allergy to tuberculin. There is general agreement that *natural resistance* should be distinguished from *acquired immunity* (Wallgren 1953). Different people and races have different powers of resistance against tuberculosis, and this natural resistance varies with the age, sex, general health, living conditions, mental and physical stress, etc. In most countries the tuberculosis mortality rate (per 10,000 of those born in a certain year) is high in infants and small children and then decreases to a low level at school age (Wallgren 1953). During puberty mortality again rises both in boys and girls. In males there is a continual rise in mortality until advanced age,

whereas in females there is an initial gradual fall after adolescence, but during the 5th decade mortality again rises. What in connection with my investigation is of interest is, however, the fact that the highest percentage mortality of those infected is to be found among infants and small children and the lowest rate in the age groups before puberty i.e. 5-10 years of age. It is estimated that natural resistance at this age is several hundred times greater than in infancy. In individuals with natural resistance the course of tuberculous primary infections usually ends with the healing of the sub-clinical primary complex. Post-primary lesions are rare and benign.

Whereas natural resistance is unspecific and inherited, acquired immunity is entirely specific, resulting from exogenous tuberculous infections, BCG included. The mechanism of this acquired immunity is, to judge from all its different features, very complicated and built up of interacting components (Malmros & Hedvall 1938, Rich 1951). Principally it seems to be bound to certain tissues (epitheloid cells). Circulating antibodies should, on the contrary, be of secondary importance (Catel and Daelen 1950). This acquired immunity seems to remain in the organism only as long as bacilli in one form or another remain.

This seems to be true also of that relative immunity which results from BCG-vaccination. The principle underlying BCG-vaccination is the substitution of a benign primary infection for a virulent and potentially malignant one (Ustvedt 1952). After such virulent primary infection acquired immunity may remain for life. The immunity following BCG-vaccination usually disappears after some years. The relation of the titer of circulating antibodies to tissue immunity is not completely understood but an acquired specific immunity can be present without any demonstrable antibodies (Wallgren 1953).

c. *Tuberculosis immunity in relation to tuberculin allergy*

Tuberculin is a mixture containing different antigenic elements of the tubercle bacillus (Schmidt 1953). The introduction into the body of living or killed tubercle bacilli usually leads to sensitivity against tuberculin. This is the case whether virulent human or bovine bacilli are introduced or vaccinations of various kinds are performed. After a virulent primary infection the resulting tuberculin allergy often lasts for life (Wallgren 1941, Jacobsson 1944) just as is the case with acquired immunity. It is estimated that annually between 0.02 per cent to 0.2 per cent of such cases become negative to Mantoux 10 TU (0.1 mg OT). (According to Larsen,

1950, this figure should be 0.024 per cent. according to *Andenaes*, 1949, 0.2 per cent.)

Tuberculin allergy is, in this connection, regarded as equivalent to sensitivity, and this does not include specific immunity as it does in the older literature (von Pirquet 1907). As a rule tuberculin allergy and immunity run parallel (Irvine 1949), but it has been frequently demonstrated that immunity may exist without clinical hypersensitivity (Chaussinand 1939, Birkhaug 1941, Widström 1941, Wilken-Jensen 1952). Sub-clinical forms of sensitivity to tuberculin (Kristensson 1942, Hyge 1947, Nielsen 1953), and latent immunity (Willis 1928, Törnell 1947, Heimbeck 1948, Wallgren 1953) are also believed to occur. It is very interesting that it has been possible to transfer local sensitiveness to tuberculin by injection of leucocytes (Chase 1945, Kirchheimer & Weiser 1947, Lawrence 1949). Thus it may be stated that sensitivity to tuberculin need not necessarily be bound to the mechanism of acquired immunity, even if these two conditions normally appear together. But from a practical point of view there has been general agreement that the tuberculin test should be used not only as a sign of the presence or absence of hypersensitivity but also as a sign of the presence or absence of specific immunity (Wallgren 1930, 1953, Birkhaug 1944, Aronson 1948, 1952, Ustvedt 1952, Wasz-Höckert 1953, Schmidt 1953, Nielsen 1953).

The tuberculin reaction is still the only practical guide of immunity following BCG-vaccination in a large clinical material. It should, of course, be theoretically possible to study those cases where clinical tuberculosis has developed in subjects who had previously been BCG-vaccinated. However, for several reasons this is hardly practicable. The number of such cases is so small, and it must also be remembered that acquired immunity following BCG-vaccination is only relative and the intensity of infection is seldom known, nor is the degree of sensitivity at the moment of exposure.

Many different kinds of technique have been used by earlier investigators (Arloing, Vidal & Le Sourd cit. Wallgren 1953) for demonstrating antibodies in tuberculosis. Lately haemagglutinins have been used (Middlebrook & Dubos 1948, Smith & Scott 1950). But as has been stated above there is no direct correlation between the degree of resistance and the antibody titre, neither has it been possible to demonstrate any correlation between sensitivity to tuberculin and the haemagglutinin titre (Lagercrantz & Enell 1953). None of the methods at present available for determining antibodies in tuberculosis are of practical use in estimating immunity to tuberculous re-infection (Aronson 1952, Sievers 1954).

d. The duration of tuberculin allergy after BCG-vaccination

It may be stated that at present only through the demonstration of tuberculin sensitivity is it possible in a large material to gain an indication of the relative immunity against tuberculosis. It is generally agreed that tuberculin sensitivity following BCG fades considerably sooner than sensitivity due to spontaneous infection (Compare page 13). Most authors, furthermore, are of the opinion that the post-vaccinal Tuberculin reaction is less pronounced than that caused by a spontaneous infection (Kristensson 1942, Heimbeck 1948, Aronson 1948, 1952). It has been shown that both the degree and duration of tuberculin sensitivity depends on the technique used, the amount of BCG-vaccine given and the size of the local reaction (Törnell 1947, Herizberg 1948, 1951, Groth-Petersen 1949, Ustvedt 1950) and that the best results are obtained with the intracutaneous route (I. A. Nielsen 1953).

Several investigators have reported on the duration of tuberculin sensitivity after BCG (Tab. 1.). The periods of observation are short and usually imperfectly followed-up. An analysis of this concerning Scandinavian material has been made by Wasz-Höckert & Donner (1953, 1954). As may be seen from the table the results vary considerably, even when the techniques of vaccination and testing have been identical. Those using oral vaccination (Feldman 1949, Rosenberg 1951) found their patients quickly became tuberculin negative (3/4 of them after 3 years) but maintained that this may be due to "desensitisation to tuberculin". As may be expected the results are also less favourable in materials where the Mantoux test has not been repeated with higher doses (100 TU or more).

Results can also be affected by other factors such as a varying risk of exposure to tuberculosis. In such materials superinfection will obviously sometimes lead to persisting hypersensitivity. Some authors, however, deny that this factor is of any importance (Andersson & Belfrage 1939). Age distribution probably also influences results (Wasz-Höckert 1948). Thus in infants hypersensitivity generally fades more rapidly. Diverging opinions concerning this matter have been expressed, and Törnell (1947) believes that, in spite of the fact that infants have less local reaction than older children, they generally retain their tuberculin allergy better than the latter. Other factors also influence the duration of tuberculin allergy e.g. the virulence of the vaccine, the dose of vaccine, the technique used in the tuberculin test, race, nutrition, social environment and various individual circumstances.

TABLE I
Percentage BTi-reverters during the first ten years following a successful vaccination with various methods.

Authors	Publ. year	Material	Vaccination method and dose mg	Tub. test up to	Years after vaccination:						Remarks	
					0	1/2	1	1 1/2	2	3 1/2	4 1/2	
Feldman	1949	Children	Concurr. oral	Mx 100 TU	1.5	6.4						
Rosenberg	1951	Infants	Concurr. oral	Mx 10 TU	37.6	64.5	74.6					
Binvik	1944	Infants	Intrac. 0.02	Mx 100 TU	20.7	66.7						
			— 0.10									
Rydén	1946	Infants	Intrac. 0.05	Mx 100 TU	1.6	6.9						
Törnell	1947	Infants	Intrac. 0.05	Mx 100 TU	10.6							
Aronson	1948	Infants	Intrac. 0.10	Mx 250 TU	9							
Rosenthal, Leslie & Loewinson	1948	Infants	Rosenthal	Mx 100 TU	11.4	14.1						
Andersson & Bellrage	1939	Children & adults	Intrac. 0.05	Mx 100 TU	3.2	4.7	2.1					
Dahl, Hertz- berg & Refsum	1941	School- children & adults	Intrac. 0.05 — 0.15	Mx 100 TU	0.6	2.4	3.2					
Winge	1942	Children & adults	Intrac.	non-exp. exp.	Mx 100 TU	6.2	14.4	26.7				
Nordvall	1944	Nurses	Intrac. 0.05	Mx 100 TU	25.8	29.8	41.8					
Törnell	1947	Children & adults	Intrac. 0.05 — 0.08	Mx 100 TU	1.8	2.3	2.8	7.7				18.5

Vonson	1948	0-20 years	Infrac. 0.10	Mx 250 TU	6.7	7.5	7.8	8.3	7.8	5.1	5.1	7.7	12.5	North Amer. Indians su perfint. fire.
Bluhm	1948	0-35 years	Infrac. 0.15	Mx 100 TU	2.3	6.3	10.8	13.3	14.5	15.3				
Eilertsen	1948	Children & adults	Rosenthal	Mx 100 TU	5.6	3.9	4.2	7.7	9.4					
Hertzberg	1948	Children & adults	Infrac. 0.05	Mx 100 TU	1	5	7	9	11	12	13	17		
Malinros	1948	Children	Rosenthal	Mx 100 TU					36					
Wasz-Höckert	1948	0-14 years	Infrac. 0.05	Mx 100 TU					0.7	4.9				
Gentz-Dahén	1949	Children & adults	Infrac. 0.05	Mx 100 TU					7.5	9.0	9.3	11.3	14.9	17.5
		Children & adults	Infrac. 0.05	Mx 100 TU										9.7
Groth-Petersen	1949	Children & adults	Infrac. 0.05	Mx 100 TU										
Gedde-Dahl	1951	Adults	Infrac. 0.05	Mx 100 TU					17.1	13.8	13.2	5.5	10.9	8.8
Enell	1952	School-children	Infrac. 0.05	Mx 100 TU										
Edward, Palmer & Magnus Nielsen	1953	School-children	Infrac. 0.075	Mx 10 TU					0					
Wasz-Höckert & Donner	1953	Children & adults	Infrac. 0.10	Mx 100 TU	6.1	7.0	9.6	8.7	9.0	19.2	26.2	4.8	14.7	
	0-31 years	Infrac. 0.05	Mx 100 TU	1.8	7.3	16.0	28.3	29.4						

As will further be seen from Tab. 1, tuberculin sensitivity after BCG-vaccination has not been systematically studied by most investigators. Data are incomplete and often diverging; thus *Edwards, Palmer and Magnus* (Denmark) as recent as in 1953 found that of 658 school children 0 per cent were tuberculin negative after 2 years, whereas *Bluhm's* figure in a material of children and adults is 10.8 per cent tuberculin negative individuals. It is interesting to note that in materials tested every year there are a greater number of reverters than in materials where the tuberculin test has been performed only once (Groth-Petersen 1949). In many general surveys of BCG-vaccination, tuberculin allergy is described as being of rather short duration: "As a rule the tuberculin reaction becomes negative after 4 years" (Birkhaug 1947, Schmidt 1953).

e. Resistance produced after BCG-vaccination

Certain standard requirements must be followed in an investigation about the use of BCG in the prevention of tuberculosis. *Irvine* (1949) has discussed these requirements, and *Park* (1947) has defined them thus:

1. Vaccine must be of standard strength.
2. There must be controls.
3. Controls and vaccinated cases should a. be selected alternately to eliminate the possibility of bias, b. have identical follow-up, c. come from the same locality, d. come from similar age group, e. come from the same social (racial) group.
4. Contact with the cases must be maintained.
5. Exposure conditions of cases must be known throughout the study period.
6. A reliable cause of death.

It has been emphasised in the introduction that in the larger Scandinavian investigations one cannot follow the suggested requirement given in point 3 a above "as it seems unlikely that physicians would deliberately withhold protection from tuberculin-negative individuals merely to obtain statistical information on the effectiveness of BCG" (Wallgren 1952). Scandinavian authors in this field all agree with this opinion.

Wilson (1947) considers that proof of resistance to tuberculous infection ought initially to be founded on comparisons of mortality, and *Levine* (1947) in this connection pointed out that by BCG-vaccination a primary complex develops in either an arm or leg—by natural spontaneous infection a primary complex is acquired in a lung which can then be revealed in the roentgenogram. This state of affairs should, thus, make a comparison of morbidity deceiving. *Wallgren* (1948) thinks that the most important thing in this connection is the invalidity caused by the primary complex and also the consequent clinical complications, the absence from

school or work due to certified disablement. In this one can include post-primary tuberculosis diseases and later on, chronic invalidity and finally death itself. Mortality will thus be the last phase of a long chain of events, although mortality might be more easily accessible for statistical purposes.

Morbidity is, however, at least as important a factor from the social, economical and other view-points, and therefore at least as valuable as a basis for comparison. This is particularly valid in countries having a low tuberculosis mortality, as in Sweden, but where in spite of this tuberculous diseases are still a problem. Here one therefore primarily turns to the tuberculosis morbidity for comparison between vaccinated and unvaccinated groups.

Concerning the early trials by *Calmette, Guérin, Weill-Hallé* the readers are referred to works cited on page 10 and 12. Here will also be found accounts of the trials performed during the first decades, often without controls or on a small scale (Wallgren 1934, Andersson & Belfrage 1939, Andersen 1941, Kristensson 1942). Some later works in this field also lack control (Winge 1949) and although it seems probable that the low morbidity and mortality described by these authors is a result of the BCG-vaccination, it is impossible to ascertain to what degree other factors may have influenced the results.

In Tab. 2 I have compiled the results of previous authors regarding the resistance produced by BCG-vaccination. In these investigations different methods and evaluations have been used and therefore the information given by me has been partly adjusted to get them commensurable. In some of the quoted papers even the primary information is incomplete, and only approximate figures available. (Tab. 2 at the end of the book.)

Where no fatal case has occurred in the BCG-group it has not been possible to compare the vaccinated and non-vaccinated groups numerically. As already mentioned Levine and Sackett (1946) did not find a lower tuberculosis morbidity in BCG-vaccinated people than in those not vaccinated. All other authors have found a definite protective effect against *primary tuberculosis*, which in most cases was statistically significant (concerning the statistical significance the reader is referred to the authors). As to the ability of BCG-vaccination to protect against or alleviate *post-primary tuberculous diseases*, some results are not specified enough to allow any definite conclusion to be drawn. Some authors have not been able to demonstrate any such ability whereas in other instances conscientiously performed investigations (Hyge 1949, Aronson et al 1952) have demonstrated statistically significant differences between vaccinated and unvaccinated groups also in this respect.

f. Superinfection

Superinfection is, according to *Scheel* (1935) a new infection coming from outside in people who have already been infected. In this sense even BCG-vaccination may be included. According to *Heimbeck* (1948) superinfection with virulent human or bovine tubercle bacilli results when the post-vaccinal allergy has subsided or disappeared. An enhanced tuberculin reaction in BCG-vaccinated individuals suggests an infection with virulent bacilli (Aronson 1948). The same author (1951) has shown that under massive superinfection the morbidity among BCG-vaccinated people is increased to the double. In *Hertzberg's* material (1948) has been included a special group of superinfection in persons previously vaccinated. He has based this on the fact that the tuberculin reaction in repeated tests has suddenly become considerably more pronounced. As has been pointed out by other investigators (Myren 1950, Nielsen 1953), this occurrence may be caused by other factors, and on the other hand one can suppose that superinfection may have occurred without an increase in the intensity of the tuberculin reaction (Wallgren 1952).

In estimating the duration of tuberculin allergy and the protective ability of BCG-vaccination the possibility that a superinfection has occurred must always be kept in mind. One or more superinfections might quite possibly increase the duration of tuberculin allergy in a BCG-vaccinated person, and in the same way a slight or moderate virulent superinfection possibly enhances the acquired immunity in an already vaccinated individual. Some authors think that the exogenous superinfection is of no great importance (Myren 1950, Kleinschmidt 1953) and *Anderson & Belfrage* (1939), furthermore, are of the opinion that the tuberculin positivity in BCG-vaccinated persons is caused by the BCG vaccine and not by superinfection.

As pointed out by several authors (Gentz & Dalén 1949, Myren 1950) this problem must be seen in relation to the general frequency of tuberculous infection. If the infection-rate is low, as in the Scandinavian countries, the rate of superinfection must also be as low or lower. An account is given in Ch. II of the risk of infection (i.e. the number of persons infected per 100 tuberculin negative individuals per observation year) in the children of Stockholm. There is a proportional relationship between the risks of superinfection and the general frequency of tuberculous infection.

CHAPTER II

Health Control, Tuberculosis and Its Management in Swedish Schools with Special Regard to Stockholm's Elementary Schools

The information in this Chapter about tuberculosis in Stockholm's Elementary schools is mainly taken from the works of **Hjärne** (1945, 1946, 1952) and otherwise from documents at the Board of the Elementary schools and the Central Tuberculosis "Dispensär" of Stockholm, and Stockholm's City Statistical Offices.

A. Children in Stockholm's Elementary Schools during the Years 1945—51

The number of children born alive in Stockholm has increased considerably, i. e. from 5,491 in 1935 to a maximum of 14,370 in 1945, and thereafter decreased; this is naturally also reflected in the size of the Elementary schools' forms. The number of children in these decreases a little because some die; others cannot, for different reasons, be taught in the Elementary schools (serious backwardness, serious chronic illness, etc.). Population changes between towns approximately counterbalance each other with regard to the concerned age groups.

Tab. 3 shows the number of children born per annum. The great increase from 1941 and the comparative decrease after 1945 is apparent, as is the number of children in the different forms of the Elementary schools, school year 1950/51. Especially after the fourth school year the above-mentioned departures to other schools occur, whereby finally the seventh and eighth forms have comparatively few children. Differences between the year groups (birth) and division into forms caused by pupils putting in a second year in the same form, etc., are small and insignificant. Fig. I with diagram also illustrates the relationship between the number of births in Stockholm to the number of children per form in Elementary school during the school year 1950/51.

B. Health Control in Schools

A school doctor is employed in each Elementary school and it is his task to safeguard the school children's health. He has the assistance of

TABLE 3

Number of children born in Stockholm during 1935—52 and number of children in the different forms of Stockholm's Elementary schools, the school year 1950/51.

Year	Number born yearly in Stockholm	Number of children per form 1950/51
		Form
1935	5,491	IX 25
1936	6,057	VIII 2,048
1937	6,318	VII 2,410
1938	7,170	VI 3,550
1939	7,767	V 4,282
1940	8,041	IV 6,504
1941	9,411	III 7,468
1942	11,083	II 9,236
1943	12,491	I 10,441
1944	14,218	Special forms 2,345*
		Total 48,309
1945	14,370	
1946	14,144	
1947	13,650	
1948	13,334	
1949	12,395	
1950	11,621	
1951	11,011	
1952	11,129	

* Children in "Aid"-, "Reading"-, Deafness- and Observation forms and Open Air forms. These were rather equally divided in forms I—VIII.

school nursing sisters. A "health card" is made out for each child immediately on starting school and this card follows the pupil from school to school until they finally leave. This card contains detailed social information plus the medical history. In the beginning it is filled up with the aid of a questionnaire sent to the parents; moreover, they are present at the first medical examination of the first form in the autumn term to answer complementary questions. Each child undergoes compulsory medical examinations in forms I, IV and VIII. In connection with these tuberculin tests are performed according to a technique described on page 37. The same technique has also been used in my follow-up. Every year during 1945—51 miniature chest radiography was done of forms I, IV and VII.

At other times the children are entitled to see the school doctor for slight

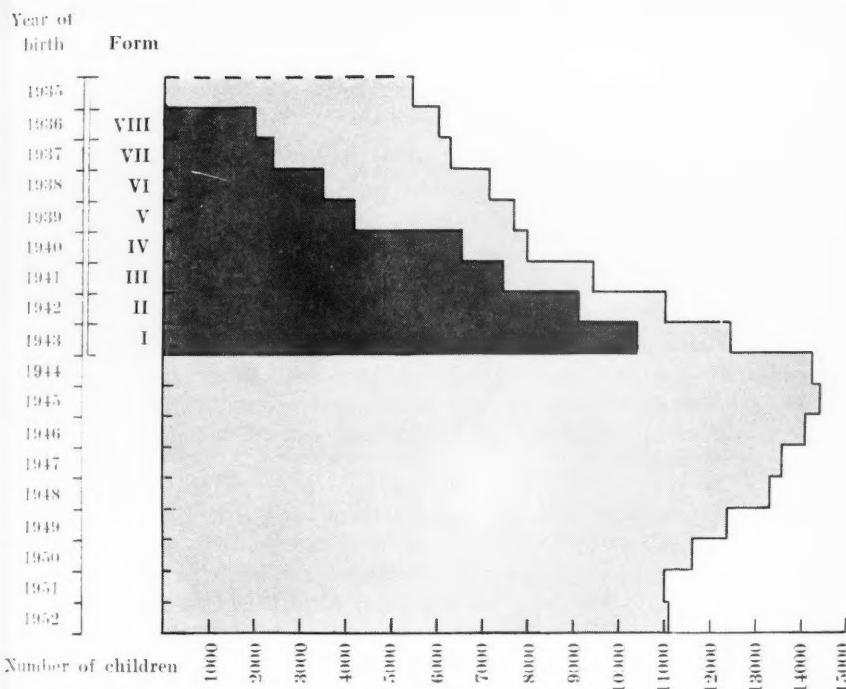


Fig. 1. Number of children born in Stockholm during 1935-52 and number of children in the different forms in Stockholm's Elementary schools, school year 1950/51.

= Number of children born in Stockholm 1935-52.

■ = Number of children attending the Elementary schools of Stockholm 1950/51

ailments or after having childish infectious diseases, and renewed tuberculin tests are made after respiratory infections. If cases of clinical tuberculosis or spontaneous inverters occur in a form, the entire form is once more examined by tuberculin tests and miniature chest radiography. The teachers and all the staff are offered a free chest roentgen control annually.

Gradually the health cards are completed as reports come to the school doctor or sister with details about the state of health. If a child of Elementary school age is admitted to a children's hospital in Stockholm for treatment, or comes to a Tuberculosis Dispensary, a summary is, in most cases, sent to the school doctor and this is attached to the health card. Thus, these health cards are reliable and almost complete. The control of

health in Stockholm's Elementary schools is watched over by the Chief School physician so everything is standardised.

C. BCG-Vaccination in the Elementary Schools of Stockholm

BCG-vaccination is entirely voluntary in Stockholm's Elementary schools and is only performed with the parents' written consent. During the school year 1942/43 it was first offered to the pupils of the final forms, but soon afterwards BCG-vaccination was performed especially on those in the first forms (7—8 years of age). From the very start it was quite clear that BCG-vaccination and the post-vaccination tuberculin test ought to be completely performed before school starts, but this has hitherto been too great a problem to organise (Hjärne 1946).

The programme for prevention of tuberculosis now shows (Tab. 4), that general voluntary BCG-vaccination has been carried out since 1945 on

TABLE 4

Scheme of prophylactic measures against tuberculosis practised in Stockholm's Elementary schools during 1943—52.*)

(According to Hjärne)

Form	Age Years	Tuberculin test	Miniature X-ray	BCG-vaccination
I	7			
II	8			
III	9			
IV	10			
V	11			
VI	12			
VII	13			Miniature X-ray
VIII	14	Tuberculin test		BCG-vaccination (Re-vace.)

*) From autumn 1952 miniature roentgen examination was performed in Form V instead of Form IV.

TABLE 5

BCG-vaccinations in Stockholm's Elementary schools during 1942—51.

Year	Total pupils in all forms	Number vacce. in all forms	Of these, in Forms	
			I—II	VII—VIII
1942/43	28,415	988	—	988
1945/46	29,165	1,435	—	1,435
1944/45	29,907	340	221	119
1943/44	31,402	1,419	3,584	835
1946/47	33,438	1,330	3,482	848
1947/48	35,278	1,765	821	852
1948/49	39,171	7,026	II—VII—VIII and forms I—VIII in 8 schools	
1949/50	43,459	5,375	5,375	
1950/51	48,309	6,706	6,706	
1951/52	52,277	6,730	6,730	
Total		39,114		

tuberculin negative school children in form I and re-vaccination on reverters and other tuberculin negative pupils as soon as there has been a possibility, at the latest in the final forms.

As the regular school nursing sisters have difficulty in getting time for BCG-vaccination in addition to their routine work, three so-called BCG-vaccination teams have been working since the Spring of 1946; each consists of two specially trained and qualified nursing sisters who circulate among the schools and assist the school doctor in charge at the vaccinations as well as tuberculin tests before and after, and with statistics, etc. This organisation has shown itself to work well. The Chief School physician sets up the time tables for miniature chest radiography and the BCG-teams.

The BCG-vaccination has been done according to Wallgren's method with 0.1—0.2 ml. vaccine (0.05—0.1 mg BCG bacilli) intradermally in the left thigh. All vaccine used has been Swedish (The BCG-Laboratory, Sahlgrenska Sjukhuset, Gothenburg). As to preparation, see *Wallgren* (1952) and *Sievers* (1954). As the question of local reactions and complications following vaccination is outside the object of this work, the author does not go into them in more detail. It should be observed, though, that a positive correlation has been proved between the size of the local reaction and percentage inverters at post-vaccination test (*Törnell* 1947, *Groth-Petersen* 1948, *Hertzberg* 1948). In my material there are no exact figures available for the local reactions and complications. The number

of inconvenient local reactions has been under 2 per cent and only a few of them have required treatment. We have aimed at clear but moderate local reactions.

Up to the Spring of 1952, 39,114 pupils from Stockholm's Elementary schools have made use of this voluntary offer. For further information see Tab. 5. There the author has also divided the children into those who have been vaccinated in the beginner's forms and those in the final forms. As can be seen, the tendency has been to more and more BCG-vaccinate the children in the first forms; this because of the generally enhanced exposure on commencing school life in comparison with the pre-school life and also because the prognosis of primary tuberculosis at puberty is comparatively bad (Hjärne 1946).

Per 10,000 inh.

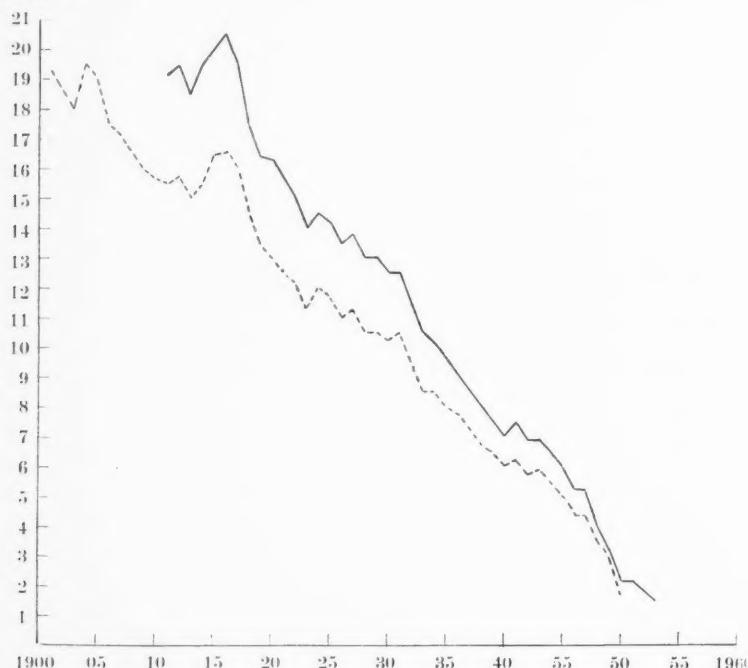


Fig. II. Tuberculosis mortality in Sweden per 10,000 inhabitants. (Swedish National Association against Tuberculosis).

— Total annual mortality.

- Annual mortality from pulmonary tuberculosis.

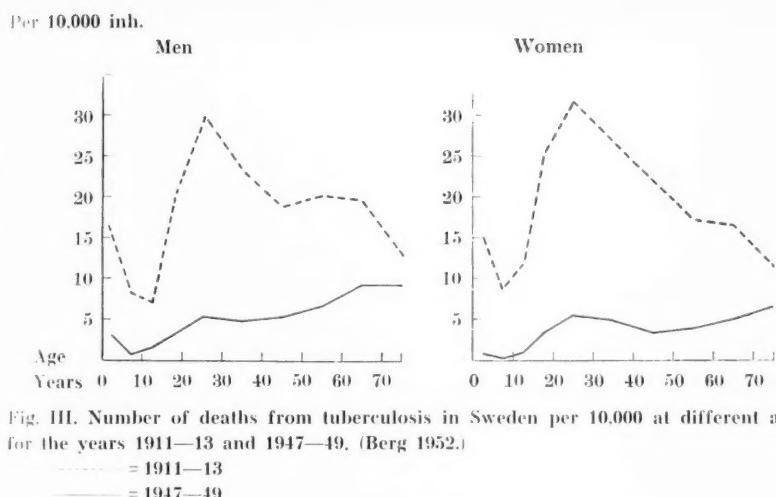


Fig. III. Number of deaths from tuberculosis in Sweden per 10,000 at different ages for the years 1911–13 and 1947–49. (Berg 1952.)

D. Open Air Forms in Stockholm's Elementary Schools

Up to 1950 there were, in Stockholm, four Open Air Elementary schools for the rehabilitation of, in all, 80 tuberculous children. Before 1945 the forms were filled and many children were obliged to wait. Since July 1950 and July 1951 respectively two of these schools have been closed while the number of children needing this kind of care continues to decrease; in the Spring term of 1951 there were altogether 42 such pupils.

E. Tuberculosis Morbidity and Mortality

a. Among children in Sweden

In Sweden the mortality from tuberculosis has gone down from about 2.5 % at the turn of the century to 0.18 % in 1952—as appears in Fig. II (Swedish National Association against Tuberculosis). It will further be noticed that the highest mortality from tuberculosis has shifted and increasingly affects older people; the maximum now being between 60 and 70 years of age; see Fig. III (Hedvall & Hillerdal 1952, Berg 1952). There is reason to suppose that this is mostly due to the tuberculous primary infections in youth decreasing in number and severity as a result of reduced risk of infection (Kristensson 1942, Berg 1952).

Per 10,000 inh.

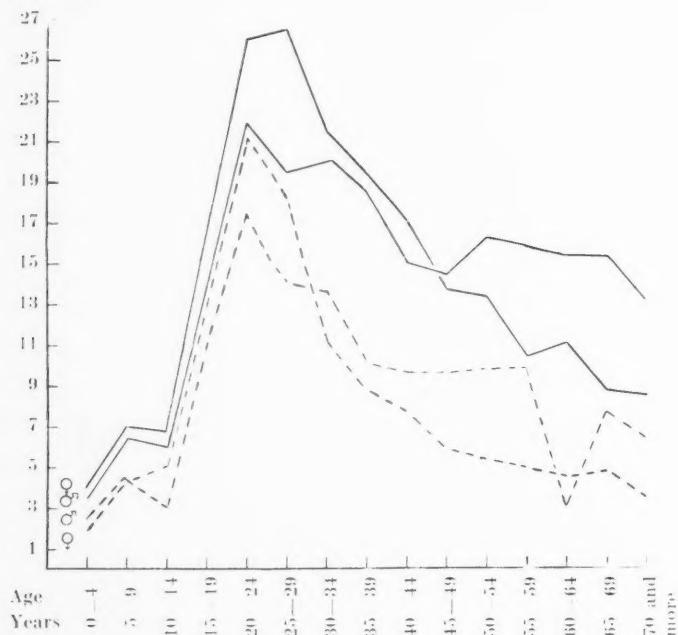
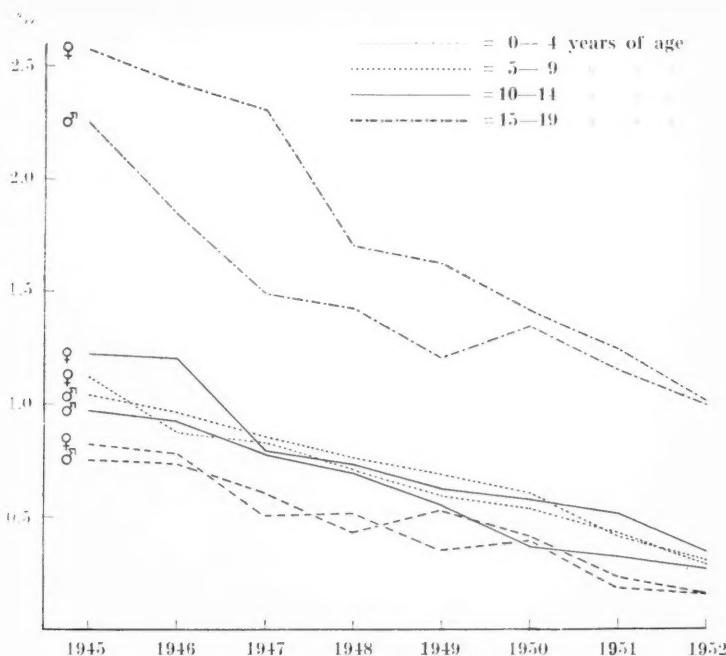


Fig. IV. Age distribution of newly diagnosed cases of tuberculosis in Sweden (registered at the "dispensärs") and patients discharged from sanatoria who have for the first time been treated there during 1951 (per 10,000 inhabitants). (Swedish National Association against Tuberculosis.)

— Newly diagnosed cases.
- - - Treated for the first time.

Regarding tuberculosis morbidity, however, the age distribution has not during the last decade shown such a big alteration. Thus, the age distribution of newly diagnosed cases in Sweden (Fig. IV) still has its maximum at the age of 20 to 30 years. In other European countries the age distribution is about the same (Schmidt 1953). Fig. V is a diagram representing the frequency of tuberculosis got from the number of children, dead or discharged improved, from tuberculosis institutions from the whole of Sweden and expressed in different age groups. The decline is marked in all age groups, e.g. 10-14 year old children from 1.10 % in 1945 to 0.55 % in 1952.



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Fig. V. Tb. patients under 20 years discharged as improved or dead from hospitals and
sanatoria 1945-52. Incidence per 1,000 of each age group (as shown).
(Swedish National Association against Tuberculosis.)

b. *Tuberculosis morbidity and mortality among Stockholm's children*

The reports from the Central "dispensär" and the Chief School physician concerning the morbidity of tuberculous diseases in Stockholm's children

TABLE 6

New cases of tuberculosis in children under 16 years of age registered at Stockholm's Central Tuberculosis "Dispensär" during 1944-50.

Year	Pulm tb.	Other tb.	Total
1944	116	242	358
1945	39	281	323
1946	103	185	288
1947	65	149	214
1948	32	201	233
1949	28	145	173
1950	10	115	125

TABLE 7

Number of children treated for tuberculosis at Stockholm's children's hospitals and sanatoria during 1945—51.

Year	In children's Hosp.	In children's Sanatoria	Total
1945	57	196	253
1946	46	193	239
1947	115	114	229
1948	101	124	225
1949	66	136	202
1950	77	117	194
1951	61	96	157

are somewhat different. Cases of tuberculosis occurring in children under 16 registered as new at the Central "dispensär" are given in Tab. 6.

An approximate idea of the tuberculosis morbidity in Stockholm among children and adolescents can be got from figures of tuberculous cases admitted to the children's hospitals and sanatoria—see Tab. 7. Because

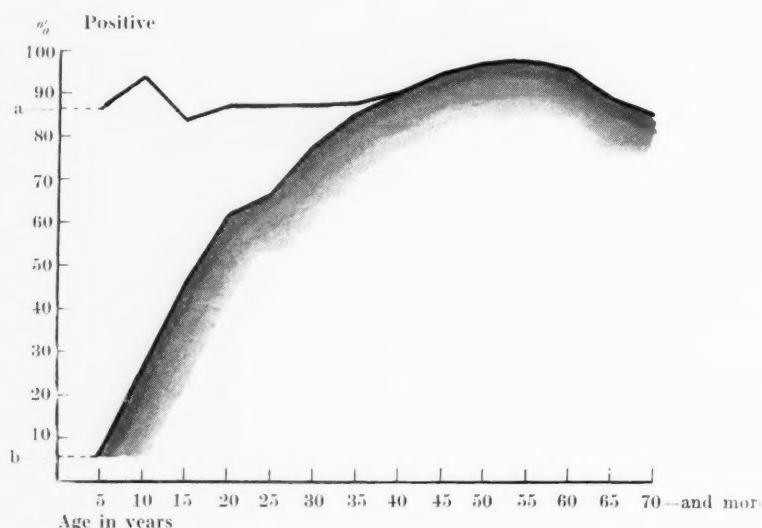


Fig. VI. Percentage of tuberculin positivity among Stockholm's inhabitants of different ages according to an investigation carried out at the "department for group vaccinations", Stockholm's Central "Dispensär", during 1949.

a = total persons BCG-vaccinated (according to their own statements) 5,464.

b = total persons not vaccinated (according to their own statements) 14,882.

TABLE 8

Mortality from all forms of tuberculosis during 1941—52 in Stockholm (Stockholm's City Statistical Office.)

Age in years	1941	1942	1943	1944	1945	1946	1947	1948	1949	1950	1951	1952	Total
0—1	6	4	2	6	3	1	2	1	—	—	—	—	25
1—5	7	10	9	6	4	5	4	1	2	—	1	—	49
5—10	3	3	5	4	5	3	3	—	—	—	—	—	26
10—15	7	6	8	5	6	2	2	—	—	1	—	—	37
Total	23	23	24	21	18	11	11	2	2	1	1	0	137

some of the children have been included in both the hospital and sanatorium groups, the totals are misleadingly high.

There is a marked decline in the total number of tuberculous cases in both tables, in spite of the increased number of children (compare Tab. 3). This decline mostly concerns primary tuberculosis, as the diminution of the total number of freshly registered cases from 1945 to 1950 is almost 2/3rds.

Regarding the frequency of spontaneous infection (inverters) in Stockholm, there is an investigation from the Central Tuberculosis "dispensär" (Fig. VI) which was carried out in 1949 by the "group vaccination department" (which has to deal with BCG-vaccination of larger groups)

TABLE 9

Division of all cases of tuberculosis occurring in Stockholm's Elementary schools 1941—52. (Chief School physician's report.)

Years	Total pupils	Erythema nodosum	Pleuritis	Prim. hilar tb.	Pulm. tb.	Other tb.	Total	Morbidity %
1941/42	28,434	28	2	66	10	8	112	3.9
1942/43	28,415	34	2	79	9	9	131	4.6
1943/44	29,165	22	?	69	8	1	100	3.4
1944/45	29,907	24	2	44	4	4	76	2.5
1945/46	31,402	25	7	45	18	3	98	3.1
1946/47	33,438	16	8	26	12	7	69	2.1
1947/48	35,278	13	6	27	20	7	73	2.1
1948/49	39,171	13	9	22	13	5	62	1.6
1949/50	43,459	3	8	22	14	5	52	1.2
1950/51	48,309	7	4	17	16	0	44	0.9
1951/52	54,277	6	2	11	16	2	37	0.7

(Gentz & Dalén 1949). From this it was found that the percentage of spontaneously positive was 6 per cent at 5 years of age and at 10 years four times as many, i.e. 25 per cent. This material is said not to have been selected. The cause of the rapid rise in spontaneous positivity in the age group 5–20 years might be that the material partly comes from mass vaccinations caused by actual cases of tuberculosis. If the risk of infection for each year of life is estimated from this curve in the age groups 5 to 20 years, it should be around 4 per cent (compare Fig. VII).

The mortality from tuberculosis among children up to 16 years of age in Stockholm is numerically small. Thus, during the five years 1947–1951, only 7 children died from pulmonary tuberculosis. The division of the mortality from tuberculous diseases in children (inclusive of pulmonary tuberculosis) is seen from Tab. 8, which, for the sake of greater lucidity, includes the years 1941 to 1952. As is seen from this table, the mortality for the ages 0–15 has, in spite of an increasing population in Stockholm, diminished from an average of 23 deaths annually to almost zero during the period 1941 to 1952. In my material there were no deaths from tuberculosis.

c. *Tuberculosis morbidity and mortality among Stockholm's Elementary school children*

In the Chief School physician's register of tuberculous diseases among the children of Stockholm's Elementary schools (Tab. 9) there is—as also in Tabs. 7 and 8—a pronounced diminution, from a maximum of 4.6 % in school year 1942/43 to 0.7 % in year 1951/52. The figures given in this table for the school years 1941/42—1943/44 are very doubtful, and certainly well on the low side on account of uncertain basic information. Since 1945 the information can be taken as comparatively correct. The cases of tuberculosis have been divided into sub-groups, and one can see that the diminution affects, above all, the primary types of tuberculosis: Erythema nodosum, pleuritis and hilar tuberculosis. On the other hand, the post-primary forms are—as far as it is possible to rely on the classification stated—diminished to a relatively lesser degree.

A conception of the frequency of spontaneous infection in pre-school and elementary school age can be got from looking at figures (from the Elementary School Board) about non-BCG-vaccinated tuberculin positive children at the first medical examination (beginners' form) and those from the fourth form. This is seen in Fig. VII, where both curves show a considerable decline and come close to 2 per cent. The occasional

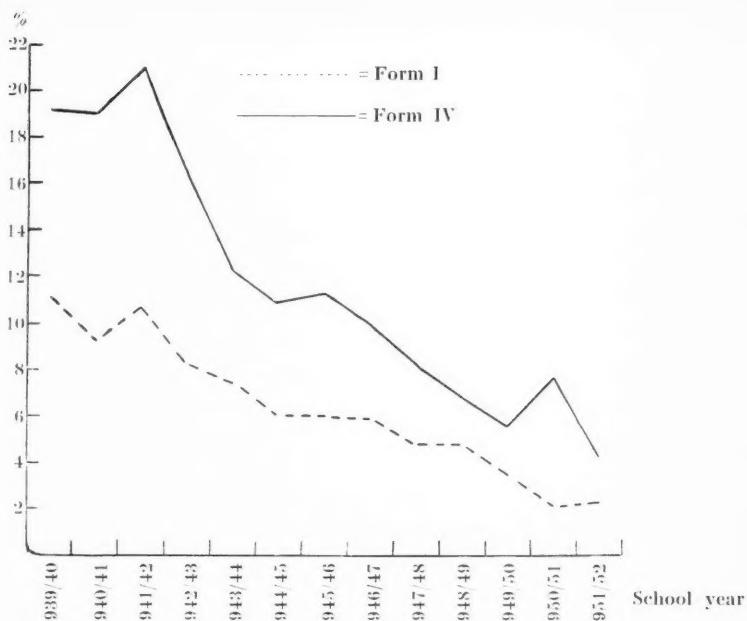


Fig. VII. Number of spontaneously positive children in Stockholm's Elementary schools when they begin school (Form I), and after four years (Form IV). Expressed as per cent of pupils in the form.

elevation, which is seen concerning the form IV, school year 1950/51, can have been caused by the more careful examination of this actual investigation. One can hopefully think that both these curves will meet, and that the occurrence of spontaneous tuberculosis during school years will come to a minimum through 100 per cent acceptance of BCG-vaccination in the first forms.

If one estimates the yearly infection risk for children of 7–10 years with the 5 year period (1947/48–1951/52) from this curve as a guide, it should be about 1 per cent. This is a quarter of that which was found as a result of the Central "dispensär's" investigation of 1949 (see above); however, because a large number of potentially spontaneous inverters have meanwhile been eliminated through BCG-vaccination in school, these percentage figures are misleadingly low.

According to previous Scandinavian experience (Wallgren 1938, Maserher 1943), about 95 per cent of all cases of erythema nodosum are

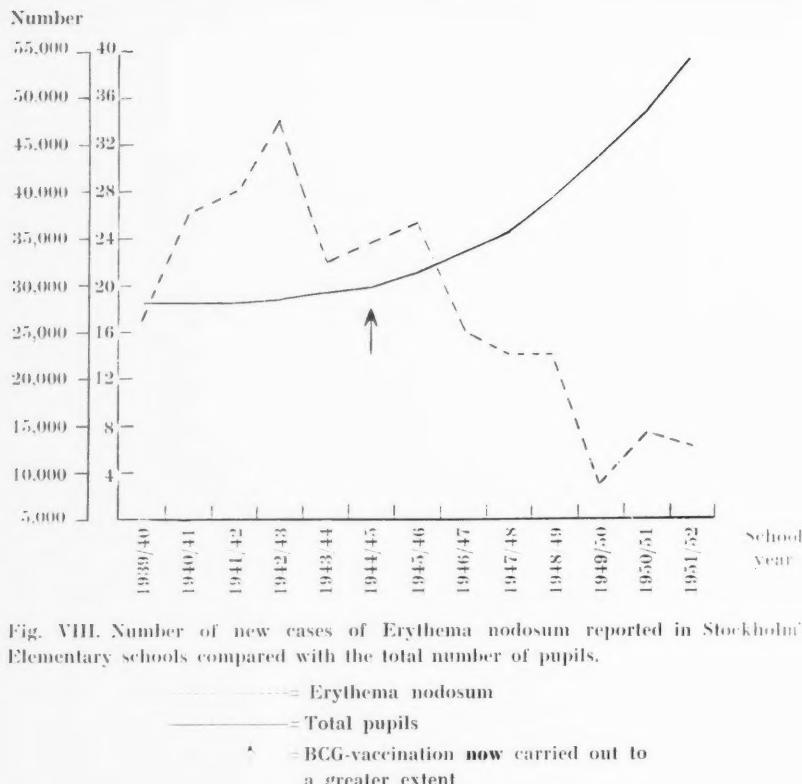


Fig. VIII. Number of new cases of Erythema nodosum reported in Stockholm's Elementary schools compared with the total number of pupils.

—— = Erythema nodosum
 —— = Total pupils
 ↑ = BCG-vaccination now carried out to
 a greater extent

tuberculous in origin among school children and those up to 20 years old. This figure may be a little too high, but anyhow, the incidence of this disease can be considered an index of the occurrence of primary tuberculosis in these ages. In Fig. VIII we can compare the frequency of erythema nodosum in Stockholm's Elementary schools with the number of pupils. In spite of the great increase in the total number of pupils the erythema nodosum frequency has diminished considerably. Completely atypical tuberculin negative cases have not been included, but a few cases, where BCG-vaccination might possibly be the cause of the erythema nodosum, are included.

Regarding the tuberculosis mortality among the children of Stockholm's Elementary schools, there are no reliable statistics before the school year 1945/46, and after this no cases were registered.

CHAPTER III

Questions concerning the Investigation

It is well known that, as earlier mentioned, the morbidity and mortality of tuberculosis is lowest in the younger school age groups. This can imply that their natural resistance is greatest at this time. This does not, however, prevent a judgement of BCG-vaccination in this age group provided that one can demonstrate a statistical difference between vaccinated and non-vaccinated groups—as comparing with a control material.

Before carrying out this investigation on school children, 9—16 years old, the author set himself questions which, if possible, were to be answered as a result of it. They were:

1. How long does a tuberculin positive reaction remain following a successful BCG-vaccination carried out during the early school years?
2. How great a difference is there between the morbidity and mortality of vaccinated and unvaccinated groups of school children?
3. What is the effect of social class and the amount of living space on the willingness for vaccination?
4. How do the two factors mentioned in question 3 affect tuberculosis morbidity?
5. How long does a tuberculin positive reaction remain following a successful BCG-vaccination carried out on the newborn in Maternity wards or during the first half year of life?

CHAPTER IV

Own Material

A. General Considerations

a. Preliminary investigation

In order to develop the method and to gain an impression of those problems which might possibly be solved by such an investigation, the author in February 1950 surveyed and tested all children in Adolf Fredrik's Elementary school, Stockholm—some 1,110 pupils aged 7—16 years. Apart from his routine work, the school doctor had every pupil in this school tuberculin tested during 1948. The result of this preliminary investigation has been previously published (Enell 1951).

b. Choice of schools

In planning this follow-up it was the author's intention to select a material representing the three social classes (see page 55) and various types of housing, so that this material would generally cover the population and living conditions of Stockholm (see Tabs. 15 and 21). Schools were therefore selected thus:—

1. a school where social class I and a high housing standard were comparatively well represented;
2. a school where social class II was well represented with housing of an older type;
3. two similar schools but housing of a more modern type;
4. one school mainly from social class III with housing of an older type, and finally
5. two schools, also primarily representing social class III, but with modern housing.

With regard to these points, the following schools were selected for the main investigation made during Spring 1951. It was natural that I had to investigate Adolf Fredrik's Elementary school again (No. 2 above). This school is situated in a fairly old part of the City and is attended mainly by children from the non-manual working class. Further, Engelbrekt's

school was chosen to represent a district where the population is fairly well off—at least from a Swedish point of view (No. 1 above). The schools of Fredhäll and Essingen are situated in districts mainly inhabited by non-manual workers (No. 3 above).

To complement these four schools, another three were selected according to points 4 and 5 above, i.e. with children coming principally from working class families. Hjorthagen's school is situated in a district where Stockholm's gas and electricity works are located, and mostly inhabited by these workers. Maria school is situated in the southern part of the city—here the housing is generally old, including some slums. Finally, Midsommarkransen's school is principally attended by children whose parents work at the L. M. Ericsson Electrical Equipment factories, and similar local factories. Housing is mixed—modern and old fashioned, but on an average it may be said to be fairly new. This totals seven schools.

In the Spring of 1951 the total number of pupils was 6,761. Only children from forms III to IX were included in the main investigation (see page 38). The number of children in these forms in the various schools is recorded in Fig. X.

B. Methods

a. Technique of tuberculin testing

Tuberculin tests in Stockholm's Elementary schools are performed with the Patch test (Hjärne 1936) and Mantoux 100 TU. The Patch test used is a modification of the Moro test. Since 1939 the following procedure has been used: The skin over the sternum is cleansed with ether and a pea-sized lump of tuberculin ointment ("Statens Bakteriologiska Laboratorium"—hereafter shortened to SBL) is applied. This is covered by a piece of adhesive plaster 2.5×2.5 cm. Another piece of the same size is used as a control in order to exclude any possible unspecific reactions caused by the plaster. The ointment base (Ung. hydrophilum) is indifferent and does not cause unspecific reactions (Silverstolpe 1954). The plaster is removed after 24 hours. After a further 48 hours the test is controlled. The Patch test has been considered positive when three or more reddened nodules or papules are found, or when there is a definite infiltration. This is in accordance with the standards applied by the Joint Enterprise (Ustvedt 1950, Holm 1950). Prior to 1946—in the case of a negative or doubtful reaction a repeated Patch test (according to Moro) was performed. Since 1946 a Mantoux test (SBL) 100 TU has been performed in such cases. This is usually read after 72 hours and is

considered positive if it gives an erythema and infiltration of at least 10×10 mm.

When the main investigation of the seven above-mentioned Elementary schools was performed in Spring, 1951, the author was aided by the BCG-teams mentioned on page 25. Nursing sisters kept the records and applied the Patch tests. With few exceptions, the author himself judged both the Patch and Mantoux tests so that he could obtain the greatest possible uniformity. The investigations were made one form at a time, and those who could not attend for the first examination were recalled later—this ensured maximum attendance, and thus reliable figures. Altogether 97.6 per cent have been completely examined.

b. Choice of forms and ages

The children from forms III to VIII inclusive were chosen for examination, i.e. those aged 8—16 years. In Adolf Fredrik's school a form IX was included. The first two forms were not included, as BCG-vaccination had been performed so recently in these children that a follow-up investigation could hardly be of great value in this connection.

At Midsommarkransen's school there is an Open Air school (see page 27), which in Spring, 1951, was attended by 16 children. In order to make this investigation representative, especially as regards the morbidity risk, this Open Air school has been included. These 16 pupils had been transferred from all schools in the southern school districts. In Spring, 1951, there were altogether 42 children in Stockholm's three Open Air schools. The total number of pupils in the southern school districts was more than one third of the total number of pupils in Stockholm's Elementary schools. Thus, the number of children attending Midsommarkransen's Open Air school was proportionately larger than would be normally expected in the seven schools studied, which more than compensates for the fact that some pupils from other schools included in this material have been referred to Open Air schools not covered by this follow-up. It was not possible to separate pupils originally coming from the seven schools from other pupils attending the Open Air schools. If these details influence the material at all, it must be in the direction of increased morbidity, both as regards vaccinated and unvaccinated children.

c. Further elaboration of the material

After completion of the tuberculin tests, the records have been compared with those of previous BCG-vaccinations made in the same forms during

1945—49 (from the records of the Chief School physician). I have studied every pupil's health card and have recorded all data of medical and sociological interest for this follow-up through annotation and punching cards according to a code. When available data have been incomplete, they have been augmented through the school nursing sisters or through contacting the parents.

As for those children who were taken ill with clinical tuberculosis, whether previously BCG-vaccinated or not, the various hospitals and the tuberculosis "dispensär" in Stockholm have kindly supplied me with copies of, or extracts from, their records. To make sure that no child who attended these seven schools during the period 1945—51 escaped the follow-up, the author has also checked with the records kept by the Chief School physician, and at Stockholm's Central "dispensär", where all children of school age who contract tuberculosis or die from it are recorded. Finally, the registers of Tjärnau's Children's Sanatorium, Stockholm, have been studied.

C. Participation in the Follow-up

The registers of forms III to IX inclusive of the seven schools included here total 4,105 pupils. Tuberculin tests were completely performed in 4,005 of these, i.e. 97.6 per cent. Thus, for various reasons, 100 pupils have not been examined: Prolonged absence from school (due to disease other than tuberculosis), prolonged leave, extensive skin diseases or serious allergy of other organs which made testing impossible. In a few cases the parents objected to the children being given injections (Mantoux). Of the 4,005 pupils who had complete tuberculin tests, 3,955 (96.3 per cent of those registered) have been included in the statistical calculation. Necessary additional information concerning 50 pupils was not available. The author has made sure that there was not a single case of clinical tuberculosis on the registers occurring in those 150 children who have not been included here.

The average age of the whole material is 10.8 years.

D. General Tuberculin Status

The general tuberculin status in the different forms appears from Fig. IX. This figure includes the whole material, whether BCG-vaccinated or not. It shows the total material as well as individual forms. As is seen, 53.1

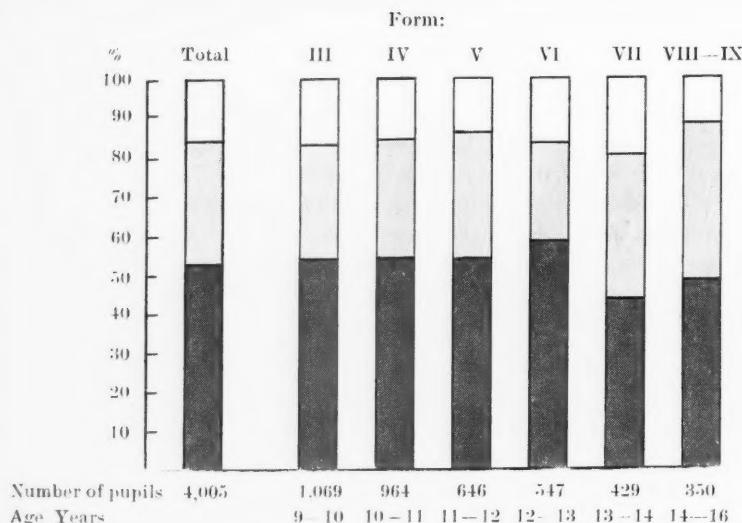


Fig. IX. Tuberculin allergy in the different forms and in the total material (Spring 1951). Dark grey = Patch test pos. (P^+), Light grey = Patch test neg. but Mx. pos. 100 TU (M^+), White = Mx.neg. 100 TU (M^-).

per cent of the children had a positive Patch test (P^+) and an additional 31.2 per cent had a positive Mantoux test 100 TU (M^+). Thus, in Stockholm in 1951 84.3 per cent of the pupils from a school material were tuberculin positive, and only 15.7 per cent had a negative reaction to Mantoux 100 TU (M^-).

On comparing the different forms (Fig. IX), it will be seen that the number of Patch test positive children (P^+) decreases somewhat with increasing age; yet this obviously does not occur to the degree which might have been expected, considering the increased thickness of the epidermis of older children.

In IT Campaigns it had been found that the Moro test is reliable up to the age of 12, i.e. there is an sufficient correlation between the results of the Moro Patch test and the Mantoux test 10 TU (Holm 1950, Ustvedt 1952, Mande & Huët 1952). Other authors (Catel & Daelen 1950, Freudenberg 1950) are of the opinion that above the age of 6 years the Patch test becomes increasingly unreliable.

As there are considerable differences of opinion on this matter, the author took special pains to register those Patch tests where there was the slightest doubt whether the test should be designated as positive or

TABLE 10

Percentage of children Mx.pos. 100 TU (M^+) at different ages of the "doubtful pos. Patch tests" ($P^?$) and of neg. Patch tests (P^-).

Form	III	IV	V	VI	VII	VIII-IX	Total
Age years	9-10	10-11	11-12	12-13	13-14	14-16	9-16
Doubtful pos. Patch test number	90	73	42	31	36	29	301
of which Mx.pos. 100 TU %							
	96.7	94.5	88.1	90.3	97.2	100	94.7
Neg. Patch test number	401	369	255	194	205	152	1,576
of which Mx.pos. 100 TU %							
	55.6	61.5	67.1	57.2	59.5	73.0	61.2

negative (pale papules, doubtful degree of infiltration, etc.) and called these "doubtful positive Patch tests" ($P^?$). Altogether there were 301 such "doubtful Patch tests" and when the Mantoux test with 100 TU was later performed, 285 or 94.7 per cent of these were definitely positive, which supports *Holm's* opinion. From a practical point of view this is important as the Patch test, owing to its simplicity, is extraordinarily suitable for mass investigations. My material clearly demonstrates that this test is very reliable in children up to the age of 16. Tab. 10 is of interest in this connection. In it the 301 "doubtful Patch tests" ($P^?$) have been divided according to age. This material is too small to enable definite conclusions to be drawn, but there is certainly a trend towards a fairly even distribution among the age groups. This table also includes the definitely negative Patch tests (P^-)—and the trend here is the same. With increasing age there is no obvious increase in the percentage of cases positive to Mantoux 100 TU (M^+).

Freudenberg (1950) and others found that a Patch test was more often positive in young school girls than in boys of a corresponding age, and *Catel & Daelen* (1950) explained this as being due to morphological differences between the skin of boys and girls. These findings were not verified in this material—the number of cases with a "doubtful Patch

TABLE 11

Percentage of Mx.pos. 100 TU (M^+) among boys and girls respectively at different ages of the "doubtful pos. Patch tests" ($P^?$) and of the neg. Patch tests (P^-).

Form	III	IV	V	VI	VII	VIII-IX	Total
Age years	9-10	10-11	11-12	12-13	13-14	14-16	9-16
Doubtful pos. ♂	54	40	22	10	21	15	159
Patch test number ♀	39	33	20	21	15	11	142
	98.0	92.5	86.4	90.0	95.2	100.0	94.3
Mx.pos. 100 TU %	94.9	97.0	90.0	90.5	100.0	100.0	95.1
Neg. Patch test number	201	207	120	71	111	70	780
♂	200	162	135	123	94	82	796
	54.7	61.4	65.8	63.4	58.6	70.0	60.9
Mx.pos. 100 TU %	56.5	61.7	68.1	53.7	60.6	75.6	61.6

test" ($P^?$) or a negative Patch test which were later found to be Mantoux positive (M^+) are evenly distributed between the sexes—see Tab. 11.

When the material is divided according to schools and forms it will be found that the state regarding tuberculin allergy is about similar both when comparing the different schools and the various forms of the same school. The variations in percentage of tuberculin positive ($P^+ + M^+$) are given in Tab. 12. The greatest difference in the whole material thus divided form by form is 23.1 per cent, i.e. statistically significant ($\chi^2 = 100^{***}$ with 41 d.f.) (Cramér 1949)¹. This difference is due to variations in the number of vaccinations in the different forms and is of no

¹ = significant on the 5 per cent level.

** = significant on the 1 per cent level.

*** = significant on the 0.1 per cent level.

TABLE 12

The percentage of tuberculin positive up to Mx. 100 TU (P^+ + M^+) in the different schools and forms.

	Form %	Adolf Fredrik	Engelbrekt	Fredhäll	Essingen	Hjorthagen	Maria	Midsommarkransen	Total Material
III	81.7	75.0	80.9	91.4	82.7	87.7	86.0	83.1	
IV	89.2	82.7	88.3	90.7	73.7	77.3	85.8	84.9	
V	90.2	80.2	93.4	89.8	85.4	78.9	88.0	86.2	
VI	90.6	77.8	92.8	94.3	88.2	76.1	81.8	84.3	
VII	81.0	82.8	84.0	87.0	91.4	74.1	77.0	80.4	
VIII-IX	89.1	84.2	96.8	91.3	77.0	88.8	91.0	88.3	
Total tub.pos.	87.0	79.6	87.3	91.0	83.2	80.6	85.0	84.3	

importance in the treatment of the whole material. If the different schools are compared, this difference is less; and if the figures for the same forms in the seven schools are added and compared, it will be seen that the maximum difference is 7.9 per cent.

The tuberculin status of the various schools is further illustrated in Fig. X, where a differentiation has also been made between Patch test positive cases (P^+) and cases who were Patch test negative but Mantoux positive 100 TU (M^+). In three of the schools the number of Patch test positive cases (P^+) was considerably larger than in the others (III = 68.5 %, IV = 70.4 % and VI = 58.7 % as compared to 41.1—45.9 % in the other schools). This is explained by the fact that a different ointment (SBL No. 44/Aug. 1950) was used in these three schools than in the other four schools (SBL No. 39/Dec. 1949). This latter ointment was prepared from Old tuberculin and stored longer; whereas the improved preparation mentioned above (SBL No. 44/Aug. 1950) utilised the same base but was prepared from a tuberculin which had been purified and concentrated by ultrafiltration (Silverstolpe 1954). For practical reasons, the tests could not be repeated; nor was this considered necessary.

From Fig. X it will also be seen that the total percentage of Patch test positive (P^+) and the Mantoux positive 100 TU (M^+) cases do not vary

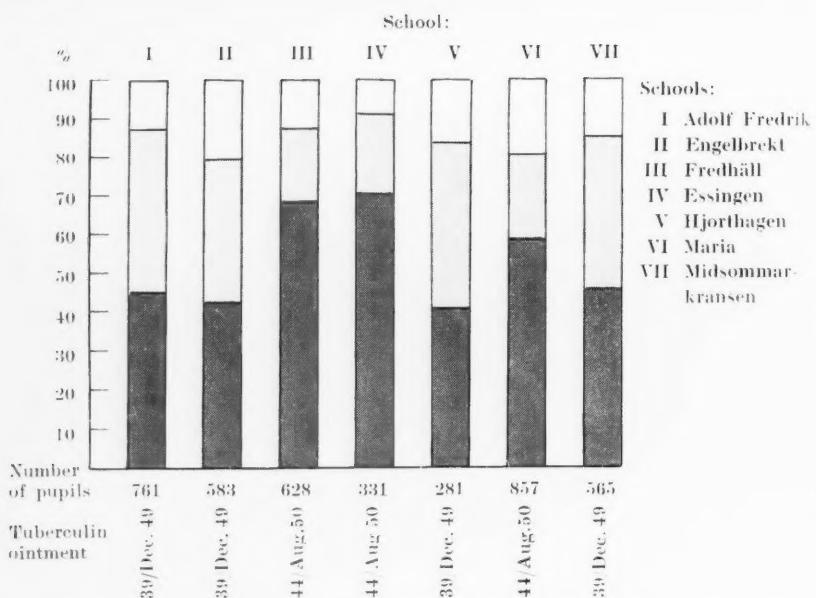


Fig. X. Tuberculin allergy in the different schools (Spring 1951). Dark grey = Patch test pos. (P⁺), Light grey = Patch test neg. but Mx.pos. 100 TU (M⁺), White = Mx.neg. 100 TU (M⁻). The SBL preparation number for the tuberculin ointment is given; all schools have used the same tuberculin solution for Mx. test i.e. No 8/51 SBL.

much in the different schools in spite of the fact that they represent separate and distinct social "groups".

E. Tuberculin Allergy in Relation to BCG-Vaccination

If the material is divided into the following categories:—1. Tuberculin negative, not previously BCG-vaccinated; 2. Tuberculin negative, previously successfully BCG-vaccinated; 3. Tuberculin positive, BCG-vaccinated, and finally 4. Spontaneously positive—it appears (Fig. XI and the survey Tab. 30) that of the 3,955 children there were 3,112 who had, at some time, been successfully vaccinated. Of these, 3,002 were still positive. This means that 78.7 per cent of the total have been voluntarily and successfully vaccinated, and that a mere 2.8 per cent had eventually reverted to negative reaction. Those who had been unsuccessfully vaccinated (i.e. were still negative on control) once or more have not been in-

School:

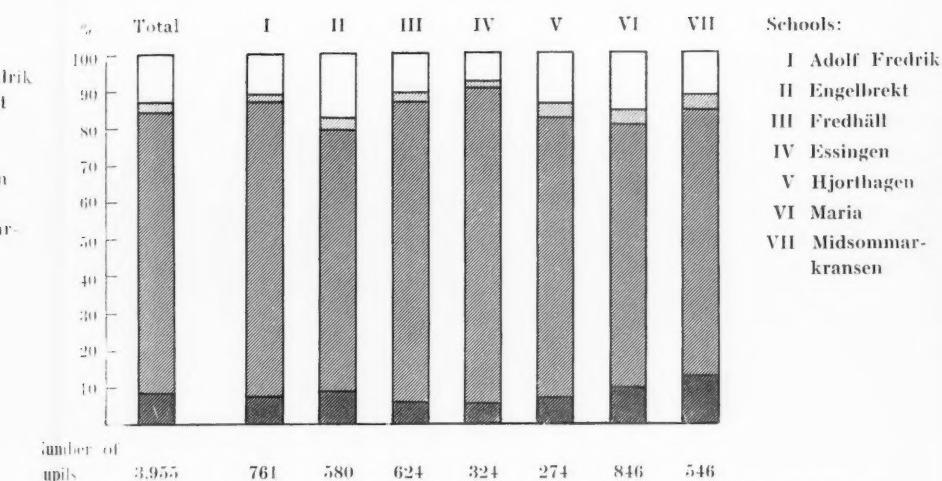


Fig. XI. Tuberculin allergy in the different schools (Spring 1951) in relation to BCG-vaccination performed. (Darkly shaded = spontaneously pos., Moderately shaded = BCG-vaccinated, tuberculin pos., Lightly shaded = previously successfully BCG-vaccinated, tuberculin neg., Unshaded = not BCG-vaccinated, tuberculin neg.)

cluded here. As will be seen from Tab. 13, the percentage of BCG-vaccinated children (2nd and 3rd categories above) varied from 59.8 per cent (Maria form VII) to 97.1 per cent (Essingen form VI); in the other forms some 70—80 per cent had submitted to vaccination. Thus, there was, on the whole, a fairly even distribution. I will later comment on the time of vaccination (see page 50 and survey Tab. 30).

It is of great interest to compare the different schools as to the degree of tuberculin sensitivity in relation to BCG-vaccination as seen in Fig. XI. Surprisingly, there is no great difference between the various schools in spite of their representing different social "groups". For reasons given below (page 56) I felt justified in grouping the first four schools together (Adolf Fredrik, Engelbrekt, Fredhäll and Essingen - school group N). This group represents a somewhat higher social level than the three remaining schools (Hjorthagen, Maria and Midsommarkransen - school group S).

There is no great difference in the degree of tuberculin positivity between these two groups—see Fig. XI. The higher figure for spontaneously positive children in Midsommarkransen's school (12.4 %) may

TABLE 13

Percentage of BCG-vaccinated children in the different forms and schools.

Form %	Adolf Fredrik	Engelbrekt	Fredhäll	Forsängen	Hjorthagen	Maria	Midsommarkransen	Total Material
III	77.8	74.0	77.5	90.2	82.4	79.1	84.7	79.7
IV	84.2	73.9	84.5	86.3	70.6	77.5	88.3	81.4
V	84.6	72.5	87.8	79.2	89.6	79.4	73.1	80.9
VI	80.2	75.9	91.2	97.1	81.4	70.5	62.6	77.2
VII	75.9	74.1	77.1	78.3	82.8	59.8	70.5	71.6
VIII—IX	76.7	68.4	80.7	85.7	68.1	79.8	68.7	75.2
Total	80.8	73.7	82.7	87.0	79.6	75.2	76.4	78.7

probably to some extent be explained by the inclusion of the above-mentioned Open Air school. Similarly the figure for Engelbrekt (8.9 %) may be influenced by the fact that an Open Air form had been previously run by this school, but was discontinued in Spring, 1950; it is conceivable that some children who were considered cured may have been transferred to ordinary forms. Of the other schools, only Maria has a comparable figure (9.2 % spontaneously positive), whereas the other schools vary between 5.3 and 7.6 per cent.

If the same forms in the different schools are added and compared with other forms, the result will be that shown in Fig. XII. Naturally, the number of spontaneously positive children increases in the higher forms. Thus, there are more than twice as many such cases in forms VIII and IX (14.4 %) as in form III (5.9 %). On the other hand, the number of reverters (successfully BCG-vaccinated, later tuberculin negative) does not increase in the higher forms.

In the Spring of 1946 *Hjärne* made a similar study of pupils in forms I, IV and VIII of the Elementary schools of Stockholm. These results have been included in Fig. XII for comparison. Five years later the number of spontaneously positive individuals had decreased considerably, especially in form VIII. Simultaneously, the number of BCG-vaccinated children had increased throughout.

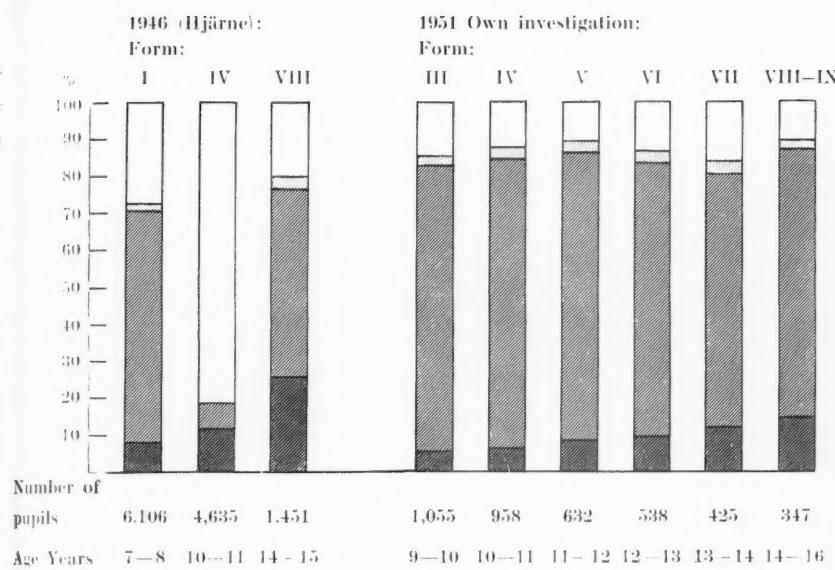


Fig. XII. Tuberculin allergy in the different forms (Spring 1951) in relation to BCG-vaccination performed, compared with a material from Stockholm's Elementary schools, Spring 1946 (according to Hjärne). (Darkly shaded = spontaneously pos., Moderately shaded = BCG-vaccinated, tuberculin pos., Lightly shaded = previously successfully BCG-vaccinated, tuberculin neg., Unshaded = not BCG-vaccinated, tuberculin neg.)

F. Non-Vaccinated Children

As has already been pointed out, the controls available in this follow-up were the non-vaccinated children. This procedure was unavoidable, although from a strictly statistical point of view it may not be absolutely correct. There were 843 such cases, constituting 21.3 per cent of the total (see Tab. 30). In the follow-up, 515, which is 13.0 per cent of the total, were tuberculin negative. Of these 515 children, the parents of 201 (5.1 %) had refused vaccination and the remaining 314 (7.9 %) had not had opportunity to join the vaccination for some reason. Of these 843 non-vaccinated children, 328 had become spontaneously positive. This group is specially described in Ch. VI.

G. Age at First BCG-Vaccination

For the following evaluation of the material, it is important to know the

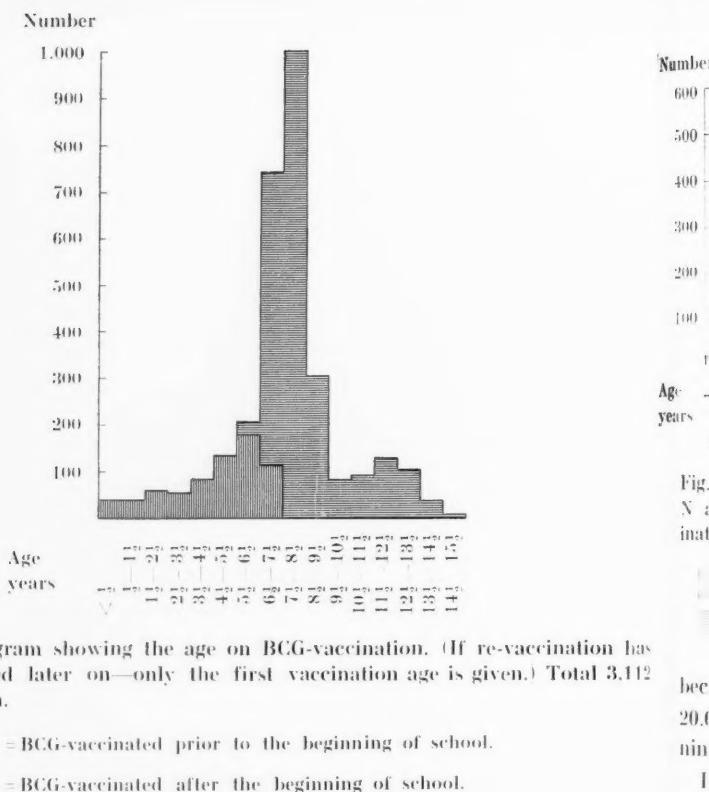


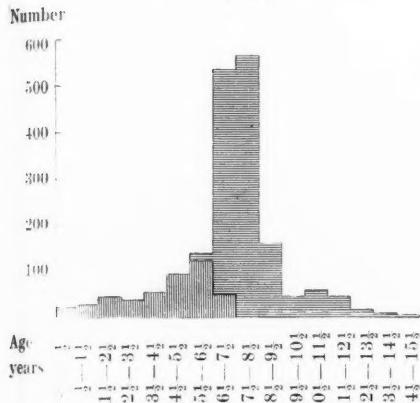
Fig. XIII. Diagram showing the age on BCG-vaccination. (If re-vaccination has been performed later on—only the first vaccination age is given.) Total 3,112 school children.

=BCG-vaccinated prior to the beginning of school.
=BCG-vaccinated after the beginning of school.

age of the children at the time of vaccination and how many had been vaccinated before starting school. As is seen from Fig. XIII, the majority—2,046 children (65.7 % of those vaccinated) were vaccinated between 7–9 years of age; and of these, 1,981 (63.7 % of the total vaccinated) were inoculated at school. The majority, altogether nearly 2/3rds., were thus vaccinated shortly after commencing school. In 78.9 per cent of instances the school was responsible for the vaccination.

BCG-vaccination was very seldom carried out in the Maternity wards in Stockholm prior to 1944, and only occasionally has such a child been included in the present material—the vaccination being performed shortly after birth and through private initiative (see Ch. VIII). In other cases, vaccination prior to school age has been performed in day nurseries, orphanages, etc., or through the "dispensär"—sometimes probably

School group N:



School group S:

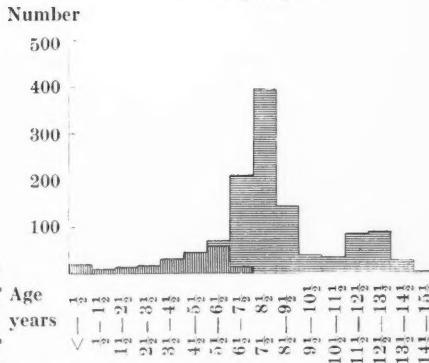


Fig. XIV. Diagram showing the age on BCG-vaccination in the two school groups, N and S. (If re-vaccination has been performed later on—only the first vaccination age is given.)

= BCG-vaccinated prior to the beginning of school.

= BCG-vaccinated after the beginning of school.

because of tuberculosis occurring in the home or environment. Altogether 20.0 per cent of the BCG-vaccinated children had this done before beginning school.

It is also of interest to see whether school groups N and S differ as to the age at vaccination. This difference is shown graphically in Fig. XIV. In school group N, 68.0 per cent were 7 to 9 years old when vaccinated, whereas the corresponding figure for school group S was 62.3 per cent. In school group S the average age on vaccination (8.3 years) was slightly higher than in school group N (7.2 years). The lower average in the latter group may be due to the higher rate of transfer to other types of schools from forms V to IX. The average age at BCG-vaccination of the whole material was 7.6 years.

H. Time of BCG-Vaccination

As previously mentioned, the initial BCG-vaccinations of the beginners in Stockholm's Elementary schools were performed during Spring, 1945.

1 — Herbert Enell

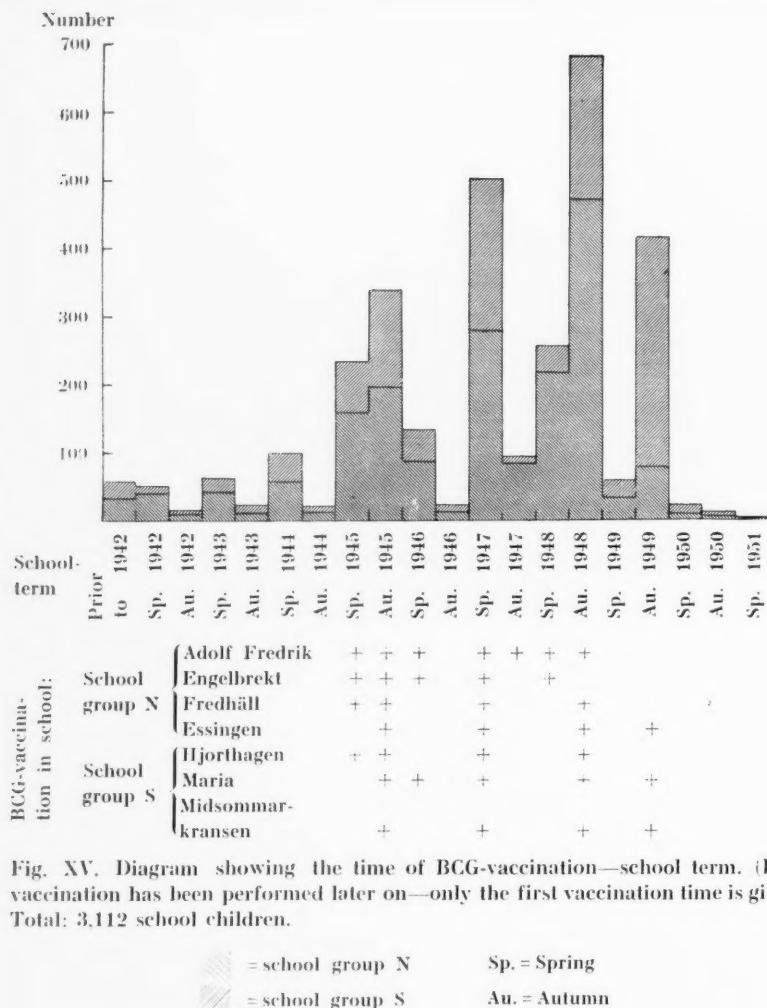


Fig. XV. Diagram showing the time of BCG-vaccination—school term. (If re-vaccination has been performed later on—only the first vaccination time is given.) Total: 3,112 school children.

As a rule, they were carried out while the children were in forms I or II. Fig. XV shows the time when the pupils were successfully BCG-vaccinated, and states if this was at school or before. No one had been vaccinated prior to 1939. When a child has been re-vaccinated following a previous successful vaccination, only the time of the first vaccination has been included (see page 98).

Mass vaccinations in schools have been performed at somewhat varying times depending on the availability of doctors and other personnel. The plus signs (Tab. XV) indicate which terms BCG-vaccination of beginners was performed in the different schools. As will be seen, vaccinations were carried out in every school during Autumn, 1945 and Spring, 1947; whereas no vaccinations were performed during Autumn, 1946 or Spring, 1949. The observation time thus varies, and for this reason the material has been divided into groups according to the time of vaccination, e.g. 233 pupils during Spring, 1945; 337 pupils during Autumn, 1945, etc. Only a very small number of children have been observed after vaccination for less than a year and a half.

Naturally, as time passes, the individual forms become very differently composed; pupils are transferred to other schools, forms are re-organised periodically, etc. These changes explain the fact that in the higher forms there are generally only a few pupils left of those originally vaccinated. However, replacements have, as a rule, been vaccinated at approximately the same time—so in practice one usually accepts the forms as they are at the time of the follow-up, and bases one's observations on this.

The time of vaccination differs little in school groups N and S (Fig. XV), and it has not been felt necessary to consider this when comparing these two school groups.

I. Previous or Current Tuberculous Environment

Tuberculosis in the family, among relatives or other possible sources of exposure through known cases (servants, lodgers, teachers, etc.) has been registered. As is shown in Tab. 14, there are no great differences between the schools in this respect. The first two categories—*tuberculin negative—non-vaccinated* and *tuberculin negative—previously successfully vaccinated*, are numerically small. For these categories, therefore, percentages have been calculated only for the whole material and school groups N and S respectively. As is seen, the percentage exposure in these categories is low—8.2 per cent in both. As the likelihood of tuberculin negative non-vaccinated children having been exposed is small, this was to be expected. This must also be true for those who revert and remain negative in spite of a previous successful BCG-vaccination. Those who have been definitely exposed are naturally more likely to belong to the other categories, i.e. *tuberculin positive—BCG-vaccinated*, or spontaneously positive.

TABLE 14

Information about previous or actual tuberculous environment in the different categories.

Schools	Tuberculin neg. non-vaccinated				Tuberculin neg. previously successfully BCG-vaccinated				Tuberculin pos. BCG-vaccinated				Spontaneously pos.	
	Number	%	Number	%	Number	%	Number	%	Number	%	Number	%	Number	%
Adolf Fredrik	10		2		83	13.7	15		25.9					
Engelbrekt	10		2		60	14.7	16		31.4					
Fredhäll	5		0		55	10.9	11		29.7					
Essingen	4		0		25	9.0	5		29.4					
School group N	29	10.2	4	8.5	223	12.4	47		28.9					
Hjorthagen	4		0		27	13.0	8		42.1					
Maria	5		3		64	10.6	21		27.0					
Midsommarkransen	4		2		46	11.6	18		26.5					
School group S	13	5.7	5	8.0	137	11.3	47		28.5					
Total	42	8.2	9	8.2	360	12.0	94		28.7					

As expected, the percentage of children exposed to tuberculosis is larger among those who have been vaccinated and are still positive (12 %), and many have been vaccinated for this very reason, or have had a superinfection (Wallgren 1953). Finally, the percentage of exposure among the spontaneously positive is high—28.7 per cent—which is also what one would expect. There is no difference worth mentioning in tuberculous environment between the two school groups. Among the non-vaccinated, tuberculin negative and spontaneously positive respectively, the difference is highly significant ($\chi^2 = 62.3^{***}$ with 1 d.f.), whereas if the vaccinated—negative and positive—are compared, no statistical difference is found ($\chi^2 = 1.5$ with 1 d.f.). Again, when the total vaccinated are compared with the total non-vaccinated (11.9 % and 16.1 % exposure respectively), the difference is highly significant ($\chi^2 = 10.9^{***}$ with 1 d.f.).

Statements by the parents, etc., regarding a tuberculous environment among those children who have had clinical tuberculosis after commencing school were made in 11 out of 42 cases, i.e. 26 per cent, which figure generally corresponds to that found regarding all spontaneously positive children (above).

In that group (f, Tab. 30) of 643 children who were tuberculin negative on commencing school and were not BCG-vaccinated, 10 per cent had a registered tuberculous environment. In the corresponding group (e, Tab. 30) of 2,458 children who were tuberculin negative on starting school and later on BCG-vaccinated, 6.7 per cent had a registered tuberculous environment. This difference is statistically significant ($\chi^2 = 8.06^{**}$ with 1 d.f.).

CHAPTER V

Social Factors

A. Introduction

"Tuberculosis is a social disease and presents problems that transcend the conventional approach.—The impact of social and economic factors must be considered as much as the mechanisms by which the tubercle bacilli cause damage to the human body" (Dubos, R. & J. 1952).

As briefly mentioned above one is well aware that numerous factors have contributed to the considerable decline of tuberculosis in Sweden, and that these are inter-connected and support each other in an indefinable way. Increased public intermingling and other factors may have caused hypothetical changes in the genetics of man and tuberculosis (Hedvall & Hillerdal, 1952 among others). More obvious factors are: compulsory medical examination of contacts "dispensär", generalised miniature screening, and generally increased medical resources—both regarding hospital treatment and the drugs themselves.

Our best aid in fighting tuberculosis, however, is to be found in the greatly improved social standard with its better hygiene, nutrition and housing—factors which must be considered as a main cause of the decreasing death rate (especially of children) and the increasing expectancy of life. When deciding what part the last decade's ever increasing BCG-vaccination's effect has played, one must accordingly keep these factors in mind so as not to overestimate the result, but get it in its right perspective.

"Inferior socio-economic status involves such aspects as poverty, poor housing and overcrowding, adverse working conditions, inferior nutrition, ignorance, superstitions, unhygienic habits, lack of facilities for isolation of cases, etc." (Vergara 1953). In my follow-up I have been able to evaluate two social factors in this connection, namely social classes and the available space in homes. Some of the observations put forward in this chapter have been previously published (Enell 1953).

B. Social Classes

a. Determination of social classes

The social class of the pupils has been estimated according to the employment of the father (or guardian) and given according to the classification used in election statistics worked out by Stockholm's City statistical offices (1948). There they now use three groups, which was thought to be less subjective than the systems that work with more than three. This grouping was used during the 1948 and 1952 general elections to the Swedish Parliament's "Second Chamber" (House of Commons). The information about employment was divided into 32 large groups, which were afterwards collected into three social classes representing the so-called upper class (I), the middle class (II), and the working class (III), respectively.

b. Division into social classes

The reasons for choosing the schools in this material so that they shall represent a cross section of Stockholm's Elementary school children I

TABLE 15

Percentage division, according to social class, of the pupils' parents or guardians in the different school groups and schools.

	Number of pupils	Social class		
		I	II	III
Stockholm according to the 1948 election statistics	—	11.5	42.5	46.0
Stockholm according to the 1952 election statistics	—	9.8	46.8	43.4
Total material	3,955	9.6	26.0	64.4
School group N	2,289	15.0	33.3	51.7
Adolf Fredrik	761	14.9	38.1	47.0
Engelbrekt	580	24.5	27.2	48.3
Fredhäll	624	7.1	33.0	59.9
Essingen	324	13.9	33.6	52.5
School group S	1,666	2.2	15.8	82.0
Hjorthagen	274	0.4	12.4	87.2
Maria	846	3.4	19.0	77.6
Midsommarkransen	546	1.1	12.6	86.3

have already given on page 36. It is seen from Tab. 15 that the present material has a lower average social classification than Stockholm's adult population according to the 1948 and 1952 election statistics. Social class III is over- and class II under-represented. The cause of this difference would seem difficult to analyse. However—it is possible that the families from social class III have more children, and that, with the passage of time, some of these families will graduate to class II. Children of unmarried mothers—placed in class III—may also effect this change.

As mentioned on page 45 it was natural to divide the material into two school groups, N(orth) and S(outh), on account of their fundamentally different social classification. This division can be clearly seen from the tables. It was made to facilitate scientific judgment, and especially so that conclusions can be drawn concerning differences between various types of living areas and the people living there. One can further see from Tab. 15 that school group N only differs slightly in its social classification from Stockholm's 1948 register of electors. In school group S there is, as was expected, a marked predominance of social class III. In the different schools of each school-group N and S, the social classification is, in the main, similar. In school group N, however, there is a noticeable difference regarding class I between Engelbrekt and Fredhäll schools.

c. *Alteration in distribution of social classes on the change from form IV to V (Departure to the "läroverk")*

A large number of the children leave form IV of the Elementary Schools for the Secondary Schools, which causes a marked change in the

TABLE 16

Shift in the percentage division of the social class at time of transfer from form IV to form V (departure to "läroverk").

		Number of pupils	Social class		
			I	II	III
Total Material		3,955	9.6	26.0	64.4
Form III—IV		2,013	15.0	30.3	54.7
Form V—IX		1,942	4.0	21.5	74.5
School- group	N	Form III—IV	21.2	35.1	43.7
	N	Form V—IX	6.6	30.9	62.5
	S	Form III—IV	3.3	21.0	75.7
	S	Form V—IX	1.3	12.2	86.5

TABLE 17

School children where vaccination was refused. Number and percentage division into social classes.

School	Total no. tub. neg. non vacc.	Refusers from these	Social class of refusers.		
			I	II	III
Adolf Fredrik	88	35	4	18	13
Engelbrekt	101	45	5	18	22
Essingen	25	9	2	0	7
Fredhäll	71	16	2	5	9
Hjorthagen	37	24	0	4	20
Maria	132	41	0	15	26
Midsommarkransen	61	31	1	3	27
Total	515	201	14	63	124
		%	7.0	31.3	61.7
Total material divided into social classes %			9.6	26.0	64.4

percentage distribution of the social classes as is shown in Tab. 16. This must be noted, although it little effects the results of the follow-up investigation.

d. Refusal of vaccination in relation to social classes

Of the 515 children who were not vaccinated with BCG and who remained tuberculin negative, it was shown that 37 per cent of the parents in school group N and 42 per cent in school group S directly objected to the vaccination. There was no marked difference between these two groups regarding their fundamental attitude against vaccination (possibly only BCG-vaccination) and on closer investigation I did not find any relation to the social classes, either. Those objecting to vaccination are found in all social classes in about equal proportions (Tab. 17). A few children who were not vaccinated for pure medical reasons are not included here.

As can be easily understood, it was not possible in the follow-up to find out reliably if spontaneously positive children were vaccination refusals or not.

e. Tuberculin allergy (vaccinated and non-vaccinated) in relation to social classes

One of the main questions of this investigation (page 35) is: How does the social class of the parents (or guardians) affect their willingness to allow their children to be vaccinated with BCG? In other words—how

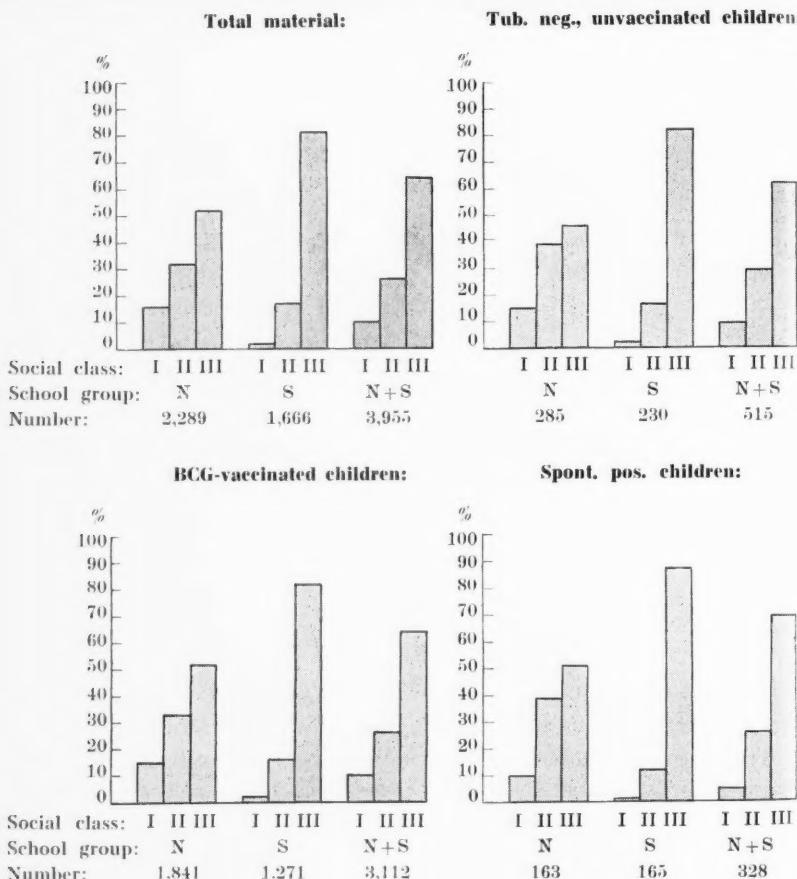


Fig. XVI. The division of pupils regarding social class and BCG-vaccination.

BCG-minded is the public? Is the interest for it—despite its voluntary character—the same in all classes of society in a city such as Stockholm? Or has it been accepted more by any one class? The answer to this question is of significance in estimating the value of BCG-vaccination. Other authors (e.g. Hertzberg 1948) have observed that the objectors to BCG-vaccination are socially and economically better off.

In order to investigate this question the material has been divided, from a medical viewpoint, into three categories: those tuberculin negative and

TABLE 18

Percentage of: 1. BCG-vaccinated and 2. spont. pos. among the unvaccinated school children with reference to the different social classes.

	Number of pupils	Number of BCG-vaccin- ated	Total % BCG-vacc.	Non-vaccinated	
				Total number	From these % spont. pos.
Form III—IV					
School group N	1,321	1,060	80.2	261	30.3
Social class I	280	237	84.6	43	27.9
Social class II	464	357	77.0	107	31.7
Social class III	577	466	80.8	111	29.7
School group S	692	561	81.1	131	31.3
Social class I	23	16	69.9	7	28.6
Social class II	145	123	84.8	22	27.3
Social class III	524	422	80.5	102	32.4
Form V—IX					
School group N	968	781	80.7	187	44.9
Social class I	64	49	76.6	15	26.7
Social class II	299	230	76.9	69	43.5
Social class III	605	502	83.0	103	48.5
School group S	974	710	72.9	264	47.0
Social class I	13	13	100.0	0	—
Social class II	119	85	71.4	34	41.2
Social class III	842	612	72.7	230	47.8
Total material	3,955	3,112	78.7	843	38.9
Social class I	380	315	82.9	65	27.7
Social class II	1,027	795	77.5	232	36.2
Social class III	2,548	2,002	78.6	546	41.4

non-vaccinated, those BCG-vaccinated and finally those who were spontaneously tuberculin positive. The relationships between these groups and the social classes are clearly seen in Fig. XVI. This Fig. seems to show that the non-BCG-vaccinated children belonging to social class III become spontaneously positive in a somewhat higher degree than those belonging to other social classes. Like in Tab. 15, a pronounced difference in distribution among the three social classes of the two school groups can also be seen. The figures of the tuberculin negative—unvaccinated and the BCG-vaccinated groups showed, in the main, a good agreement.

The slight shift among the spontaneously positive children towards a

lower social class is more clearly shown in Tab. 18. This table shows the percentage of vaccinated school children belonging to the different social classes of the two school groups. It has, in addition, been further divided into forms III and IV, and V to IX respectively. The percentage total vaccinated within these social classes is remarkably equal and no testing is necessary. This table also gives the total non-vaccinated school children and the percentage of these who have become spontaneously positive; even here a division into form- and school-groups is made. This column shows a slight tendency towards a greater percentage of spontaneously positive children in the lower social classes; thus, in the total series 27.7 per cent in social class I, 36.2 per cent in social class II and 41.4 per cent in social class III. There is, however, no significant difference here. If the social classes are tested against one another statistically, regarding forms III & IV ($N + S$) one gets $\chi^2 = 0.18$ with 2 d. f., not significant. The same check between social classes for forms V to IX ($N + S$) gives $\chi^2 = 3.24$ with 2 d.f., not significant. For an equivalent check of the whole material one gets $\chi^2 = 2.05$ with 2 d. f., not significant.

It might be assumed that those pupils from the social classes I and II who developed clinical tuberculosis have subsequently been placed in different types of schools than Elementary schools. This assumption, however, is not supported by the figures which show a similar distribution of spontaneously positive children in forms III—IV and V—IX.

Conclusion: One is thus entitled to conclude that BCG-vaccination is embraced to a similar extent by all the social classes of Stockholm.

The relatively slight and non-statistically significant differences in the percentage of spontaneously positive children between the different social classes implies that in Stockholm tuberculosis can no longer be labelled a "disease of the poor".

C. The Available Space in Homes

a. *Questions to be answered*

In order to check the relationship between social factors and BCG-vaccination from a further viewpoint, the size of the pupils' homes has also been investigated. This has been mentioned previously. How big a part has the generally raised housing standard played in the marked decline of tuberculosis in Sweden during the last decades? One cannot hope to get a definite answer to this question, but it ought to be possible to show how the housing standard of the spontaneously positive children

compares with that of the non-infected, and also how this housing standard effects the willingness for BCG-vaccination.

b. Estimation of the available space in dwellings

Information about this is given on every pupil's health card at the Elementary schools. There one can find the total number of rooms (living-room, kitchen etc.) and in addition how many members of the family (and of other people) are living there. The recording of this available space has been carried out according to the criteria for overcrowding, which have been quoted by the Swedish Government's Official Investigation, "Bostadssociala utredningen" 1945, on this subject. There, two persons per room (excluding kitchen) is considered normal, counting infants and small children as adults. The kitchen has not been included as a sleeping place, as one can suppose that the time of the so-called "living kitchen" is over. Those families where four or more persons live in the same room have been designated "overcrowded", three people per room "crowded", and less than three persons per room as "families with good space". This "space definition" has become the measure of the standard of the living quarters, even if what is meant by overcrowding is, within certain limits, dependent on subjective judgement. In my evaluation of housing I have been satisfied to use available space as my yardstick—and have not counted with hygienic standard, modernity, comfort, etc. of flats. The estimation of these latter factors is even still more subjective, and furthermore it is more difficult to get information about them.

c. Division of the material according to the amount of living space

The division of the material according to the amount of living space (as described above) is made clear in Tab. 19. It is seen that a half of the pupils had a satisfactory housing standard, and that 1/5th of them were overcrowded. Overcrowding was greater in school group S, and most pronounced in Midsommarkransen's School, where a mere third of the children had satisfactory living space. Overcrowding generally varied much between the different schools.

According to the "Official Counting of Flats" of Stockholm in 1950, 42.7 per cent of children under 15 living in the centre were crowded, and equivalent figures for the whole city were 32.8 per cent. These percentage figures were obtained through a 1/10th sampling. The last-mentioned calculation takes the same criteria as a basis as does this investigation, and as the author found a 49.6 per cent incidence of crowding of the

TABLE 19

Percentage division into groups regarding available space in homes within the different school groups and schools.

	Number of pupils	Good space	Crowded	Over-crowded
Total material	3,955	50.4	30.4	19.2
School group N	2,289	59.0	23.5	17.5
Adolf Fredrik	761	64.0	21.8	14.2
Engelbrekt	580	64.7	22.9	12.4
Fredhäll	624	51.9	26.9	21.2
Essingen	324	50.6	22.2	27.2
School group S	1,666	38.7	39.8	21.5
Hjorthagen	274	37.6	37.9	24.5
Maria	846	41.5	40.9	17.6
Midsommarkransen	546	35.0	39.0	26.0

pupils in this material—who live especially in the central part of the city—it seemed that these figures were in tolerably good agreement. It was not possible to get any direct comparative figures of similar material.

Information about the sub-division “crowded—overcrowded” for Stockholm is not available. There is, however, certain information regarding crowding in general for each “parish” (administrative district), also for the suburbs and the city centre and finally for the whole city—referred to in Tab. 20. Overcrowding in families with children in these districts is most pronounced in the outer areas, where it affects 35—50 per cent of all inhabitants. It must be noted that the areas from which the schools get their children do not coincide with the “parish” limits.

If one compares the official figures given in Tab. 20 with the standard of housing stated for this material (see Tab. 19), one is struck by certain differences. Overcrowding is consistently more common in families with children of school age. Furthermore, in certain areas in the city centre (Adolf Fredrik, Engelbrekt) there is approximately a threefold increase in overrowing as compared with the total population. In the surrounding districts (Essingen, Midsommarkransen) the difference is relatively less, but, on the other hand the percentage of overcrowding for the whole population is considerably higher (35—50 per cent). Only in the Essingen district is the percentage of overcrowding the same in both tables, which may be explained by the fact that this part of the town is relatively newly built and largely inhabited by families with young children. The official

TABLE 20

Available space for some "parishes" (administrative districts) of Stockholm according to "Official Counting of Flats" 1950 (Stockholm's City statistical offices).

"Parishes"	Inhabitants	Average number of persons		Crowding*)	
		per flat	per room	Number	per cent of all inhabitants
City centre	408,201	2.38	0.91	84,989	20.8
S:t Göran (Fredhäll)	49,548	2.38	1.05	13,926	28.1
Adolf Fredrik	13,622	2.52	0.82	1,414	10.4
Engelbrekt (incl. Hjorthagen)	27,447	2.59	0.77	3,724	13.6
Maria	20,000	2.41	0.91	4,313	21.6
Surrounding districts	307,749	3.12	0.99	62,288	20.2
Midsommarkransen	15,530	2.93	1.14	5,441	35.0
Stora Essingen	6,632	2.91	1.03	2,345	35.4
Lilla Essingen	5,939	2.59	1.26	2,984	50.2
Whole city	715,950	2.65	0.94	147,277	20.6

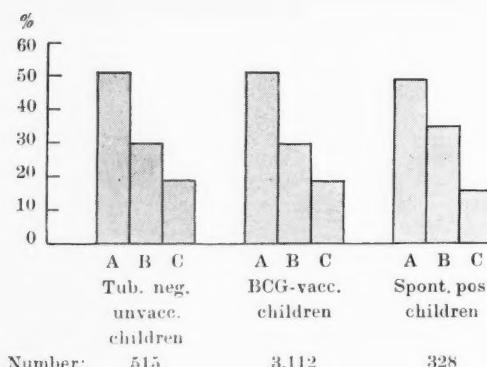
*) more than 2 persons per room excluding kitchen

statistics, however, do not offer a fair comparison with the author's so-called school groups.

d. Tuberculin allergy (vaccinated and non-vaccinated) in relation to the amount of living space

Fig. XVII shows the relationship of available space in homes to BCG-vaccination. The same division of the material has been used as in the investigation of the relationship: Social class/Tuberculin allergy and BCG-vaccination. As is seen, the amount of living space is nearly identical for the categories tuberculin negative non-vaccinated and BCG-vaccinated children. Among the spontaneously positive the group "overcrowded" is 3 per cent lower and the percentage of "crowded" is 5 per cent higher. These differences are not statistically significant.

With a more detailed, tabulated correlation between the degree of



Criteria for overcrowding:

(according to the Swedish Government's Official Investigation, 1945).

- A = Good space < 3 pers. per room
- B = Crowded = 3 pers. per room
- C = Overcrowded > 3 pers. per room

Fig. XVII. Pupils' standard of housing (available space).

living space and the percentage both of vaccinated pupils and of those spontaneously positive who were not vaccinated (Tab. 21), one can see that there is a percentally slightly greater number of spontaneously positive children in school group S, forms V—IX. On the other hand, there is hardly any difference between the younger forms of the two school groups. This table shows even more convincingly than Fig. XVII that the figures for the different housing categories are remarkably alike. In a few groups there is even a somewhat higher percentage of spontaneously positive among the "crowded" or those with a "good space" than among the "overcrowded". This distribution is surprising, but the following reservation ought to be given. Bigger and more modern flats may have been acquired after the occurrence of spontaneous positivity, or perhaps for this very reason (tuberculosis in the family) through the help of the "dispensär" (housing priority, etc.). The difference in the division of the space available in homes is so small both between school and form groups that it is of no significance. If the entire material is tested for this difference it is found to be $\chi^2 = 2.05$ with 2 d. f., not significant. It is also seen from Tab. 21 that the percentage of those vaccinated is fairly equally distributed among the groups with different housing standards, both in regards to the total as

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TABLE 21

Percentage of: 1. BCG-vaccinated and 2. spont. positive among the non-vaccinated school children in relation to different standards of space available in the homes.

	Number of pupils	Number of BCG-vaccin- ated	Total % BCG-vacc.	Non-vaccinated	
				Total number	From these % spont. pos.
Form III—IV					
School group N	1,321	1,060	80.2	261	30.3
Good space	814	645	79.2	169	31.4
Crowded	281	229	81.5	52	25.0
Overcrowded	226	186	82.3	40	32.5
School group S	692	561	81.1	131	31.1
Good space	291	242	83.2	49	28.0
Crowded	255	201	78.6	53	35.8
Overcrowded	146	118	80.8	29	27.6
Form V—IX					
School group N	968	781	80.7	187	44.9
Good space	536	425	79.3	111	44.1
Crowded	258	206	79.8	52	46.2
Overcrowded	174	150	86.2	24	45.8
School group S	974	710	72.9	264	47.0
Good space	356	267	75.0	89	48.3
Crowded	408	292	71.6	116	50.9
Overcrowded	210	151	71.9	59	37.3
Total material	3,955	3,112	78.7	843	38.9
Good space	1,995	1,577	79.0	418	38.0
Crowded	1,202	929	77.4	273	42.1
Overcrowded	758	606	80.0	152	35.5

well as the form and school groups. This is in accordance with what was found concerning the social classes in Tab. 18.

Conclusion: If anything can be said, there are a few less "overcrowded" pupils within the spontaneously positive category than in the other BCG-vaccinated and non-vaccinated groups of school children, but this difference was not statistically verified. In all circumstances overcrowding is not greater among the tuberculous children, not even in any sub-group.

TABLE 22

Percentage division in "available space" groups within the different "form groups", school groups and social classes.

	Number of pupils	Good space	Crowded	Overcrowded
Form III—IV				
School group N	1,321	61.6	21.3	17.1
Social class I	280	97.5	2.5	—
Social class II	464	77.2	15.3	7.5
Social class III	577	31.5	35.2	33.3
School group S	692	42.1	36.8	21.1
Social class I	23	91.3	4.35	4.35
Social class II	145	66.9	21.4	11.7
Social class III	524	32.6	42.6	24.8
Form V—IX				
School group N	968	55.4	26.6	18.0
Social class I	64	93.8	6.2	—
Social class II	299	76.9	16.4	6.7
Social class III	605	40.8	33.9	25.3
School group S	974	36.5	41.9	21.6
Social class I	13	76.9	23.1	—
Social class II	119	73.1	20.2	6.7
Social class III	842	30.8	45.2	24.0

D. Social Class in Relation to Available Space in Homes

From a purely sociological viewpoint it is of interest to compare the social class with the degree of space in the homes. This comparison is illustrated in Tab. 22, where the children have also been divided into form and school groups. As could be expected there were only a few overcrowded homes within social class I, nearly 30 per cent in social class II, whereas the third social class usually had some 60—70 per cent overcrowding. School group N is considerably more favoured with good living space in the homes than school group S.

CHAPTER VI

Clinical and Subclinical Tuberculosis within the Material

A. Morbidity from Tuberculosis among Non-Vaccinated School Children

a. Division into subclinical and different types of clinical tuberculosis

Of the 843 children in this research material who were not BCG-vaccinated, 38.9 per cent or 328 were spontaneously positive (so-called inverters). The primary infection (clinical or subclinical) might have taken place before or during the school period. This was 8.3 per cent of the whole material. The average age of this material was 10.8 years. This figure, 8.3 per cent, differs rather greatly from that figure for the corresponding age group obtained in the 1949 investigation of the Central Tuberculosis "Dispensär", i.e. 25 per cent at 10 years of age (see page 32). This difference is obvious, even if taking into consideration BCG-vaccination. A direct comparison is, however, not possible, as the latter figure (25 %) relates to a year-group, and the former (8.3 %) to a group of school children of 7—16 years. Out of my 328 children (inverters) 178, or 54.3 per cent had not shown any clinically verified localised tuberculosis (see Tab. 23). Thus, their primary tuberculous infection and tuberculin-inversion had apparently, and according to the history, passed without any effect on general condition, temperature, SR or any pathological findings from the lungs including pulmonary roentgen examination. Any other clinical care than further observation had not been necessary.

Tab. 23 shows that the percentage of spontaneously positive children without clinically localised tuberculosis among those non-vaccinated is comparatively similar from one school to another. The percentage of children with clinically localised tuberculosis, however, varies more and is higher in school group S. The division of the spontaneously positive children in localised and non-localised tuberculosis within the different schools also appears in Tab. 23. The author has also in this table made a comparison between the different school groups in this respect. It then

TABLE 23

Spontaneous positivity with and without verified localised tuberculosis resp. among non-vaccinated children in the different schools and school groups.

School	Non-BCG-vaccinated children					
	Number	Spontaneously positive				% with clin.tb. of spontan- eously pos.
		Without clin.tb.	With clin.tb.	Number	%	
Adolf Fredrik	146	36	24.7	22	15.1	37.9
Engelbrekt	152	34	22.4	17	11.2	33.3
Fredhäll	108	23	21.3	14	13.0	37.8
Essingen	42	8	19.0	9	21.4	52.9
School group N	448	101	22.5	62	13.8	38.0
Hjorthagen	56	9	16.1	10	17.9	52.6
Maria	210	41	19.5	37	17.6	47.4
Midsommarkransen	129	27	20.9	41	31.8	60.3
School group S	395	77	19.5	88	22.3	53.3
Total material	843	178	21.1	150	17.8	45.7

appears that the percentage of children with localised tuberculosis is 15.3 per cent *higher* in school group S than school group N. This could partly be due to the previously-mentioned Open Air school in Midsommarkransen Elementary school, but the difference is, however, too great for this to be the only explanation. This difference is statistically significant ($\chi^2 = 7.73^{**}$ with 1 d.f.). The conclusion must thus be drawn that, the tuberculous disease within those areas from which school group S pupils are taken, because of one or some factors, should have a more serious form. The difference as to stated former or present tuberculous surroundings is, according to Tab. 14, non-existent, and even if these statements are somewhat unreliable, this factor in this respect could be eliminated.

The division into social classes is very different in the two school groups and according to page 60 I have shown a non-statistically significant shift among the spontaneously positive towards a lower social class in the total material. The fact that school group S contains a higher percentage of clinical forms of tuberculosis possibly has to be considered in this connection. Besides, it might be possible that the observation of children from social class I is better, so that tuberculous disease is not so easily overlooked. Then this difference gets still greater, as some possible cases

from social class I are included, which in social class III might not have been recognised as a disease, but as a spontaneous tuberculin inversion. Tab. 24 illustrates the above-mentioned conceptions. There the distribution into social classes is given for children with clinical tuberculosis; i. for each school group separately, and ii. for the total material, and compared with the social class distribution of the whole material (see page 55). In school group S this distribution is, in the main, similar among the social groups ($\chi^2 = 0.32$ with 2 d.f.) but in school group N, on the other hand, there is a tendency for the cases of clinical tuberculosis to shift from social class I to II ($\chi^2 = 7.92^*$ with 2 d.f.). Social class III has about the same frequency as in the total material. This shift towards lower social class is also seen to be valid in the total material, and is statistically significant (N + S: $\chi^2 = 10.65^{**}$ with 2 d.f.).

By analysing the different forms of clinical tuberculosis existing among the 150 children according to Tab. 25, one will find that prim. pulm. tuberculosis is entirely dominating numerically, especially in school group S. There is also seen a difference regarding post primary pulmonary

TABLE 24

Social class division of children with clinical tuberculosis in the two school groups, as compared with the whole material.

		Number	Social classes		
			I %	II %	III %
School group N	Total children	2,289	15.0	33.3	51.7
	Cases with clin. tb.	62	3.2	43.6	53.1
School group S	Total children	1,666	2.2	15.8	82.0
	Cases with clin. tb.	88	2.3	13.6	84.1
Total Material	Total children	3,955	9.6	26.0	64.4
	Cases with clin. tb.	150	2.9	26.0	71.3

tuberculosis between the two school groups. School group S has percentually almost twice as many such cases, but the absolute number is too small and the difference is not statistically significant. Out of the different forms of clinical tuberculosis, 91.3 per cent consist of primary tuberculous cases.

TABLE 25

Different forms of clinical tuberculosis among non-vaccinated children in the different schools and school groups. (In 21 cases there is a co-existence of different forms of clinical tuberculosis.)

School	Non-BCG-Vaccinated Children						
	With clin. tb. Number	E. N.	Prim. pulm. tb.	Tb. pleur- itis	Post prim. pulm. tb.	Tb. cervical adenitis	Tb. spondy- litis
Adolf Fredrik	22	2	19	2	0	1	0
Engelbrekt	17	2	14	2	1	0	1
Fredhäll	14	2	14	1	0	0	0
Essingen	9	0	6	2	2	0	0
School group N	62	6	53	7	3	1	1
%	100.0	9.7	85.5	11.3	4.8	1.6	1.6
Hjorthagen	10	2	9	0	0	0	1
Maria	37	7	32	2	3	0	0
Midsommarkransen	41	5	32	3	4	0	0
School group S	88	14	73	5	7	0	1
%	100.0	15.9	83.0	5.7	8.0	0	1.1
Total material	150	20	126	12	10	1	2
%	100.0	13.3	84.0	8.0	6.7	0.7	1.3

b. *The intensity of tuberculin sensitivity in children with and without clinical symptoms*

It has since long been known (Heimbeck 1948, Hertzberg 1948 among others) that the degree of tuberculin sensitivity is, to a certain extent, a measure of the severity of the infection, and some authors (Aronson 1952) consequently consider themselves justified in making direct conclusions

TABLE 26

The intensity of the tuberculin reaction among spontaneously positive children without and with clinical tuberculosis resp.

	School group N	School group S	Total
Spont. pos. without localised tb. (total)	101	77	178
From these Patch test neg. with pos. Mx 100 TU (M ⁺)	34	30	64
Percentage Patch test neg. with pos. Mx 100 TU (M ⁺) of all spont. pos. without localised tb.	33.7	39.0	36.0
Spont. pos. with clinical verif. tb. (total)	62	88	150
From these Patch test neg. with pos. Mx 100 TU (M ⁺)	4	8	12
Percentage Patch test neg. with pos. Mx 100 (M ⁺) of all spont. pos. with clinical tb.	6.5	9.1	8.0

as to course, infection "dose", superinfection etc. I have compared the intensity of the tuberculin allergy in those pupils who have inverted without clinically localised tuberculosis, with the intensity in those who have shown clinical tuberculosis. It then appears from Tab. 26 that in the latter group there is a considerably greater number who react distinctly positively at the initial Patch test, so that the percentage of those positive to the Patch test among the spontaneously positive without localised tuberculosis amounts to 64 per cent and is as high as 92 per cent among those who have shown such clinical symptoms. This difference is statistically significant ($\chi^2 = 35.7^{***}$ with 1 d.f.). As could be expected, there is no noteworthy difference between the school groups N and S in this respect.

c. Time when inversion occurs

The actual time for the occurrence of spontaneous positivity to tuberculin has its special interest. In 148 cases this inversion was known before school began. See further Tab. 27 and the survey in Tab. 30. Of the 328 spontaneously positive children, a further 80, i.e. 24 per cent had their tuberculin inversion revealed at the first school examination or during the

first school year. One must, however, admit that there is a possibility that some of the first category might have been tuberculin positive a rather long time but that they have not been earlier tuberculin tested.

Of the non-BCG-vaccinated children, 20 per cent have been spontaneously positive and 6.5 per cent have shown symptoms of clinical tuberculosis after the beginning of school.

TABLE 27

Among the spontaneously positive children has the tuberculin inversion been proved:

	Number	Per cent
Prior to school	148	45.1
At the first school medical examination	52	15.9
During the first school year	28	8.5
Later, during 2nd—8th school year	100	30.5

B. Tuberculosis Morbidity among BCG-Vaccinated School Children

a. Clinical tuberculosis in previously BCG-vaccinated children

Of special interest are those children in this material who, in spite of previous successful BCG-vaccination, have got clinically verified tuberculosis. Several authors have written in more detail on similar material (Immerslund 1943, Ustvedt 1950, Alexandre 1952). Some authors (Kristensson 1942, Rinvik 1944, Ferguson 1946, Hyge 1947, Heimbeck 1948, Wallgren 1948, 1953, Rosenthal et al 1948, Dahlström & Difs 1951, Ustvedt 1952) have emphasised that such cases should not only be increasingly scarce but also present a milder form of primary tuberculosis. Others have speculated a lot about whether tuberculin sensitivity and/or immunity has been completely extinguished before the actual time of exposure, as well as the importance at a superinfection of a more or less massive dose of tubercle bacilli.

The author has painstakingly tried to trace those cases who possibly could be classified under this heading, and he has been very strict in the judgement of this—which is why even suspected cases have been included. Both the Tuberculosis “Dispensär” in Stockholm and the Chief School physician have, from their reports, constructed a special card register for

cases of this kind occurring in Stockholm's schools, and I have gone through these as well as the paper of Alexandre (1952) which deals with Stockholm's children.

The scientific investigation of a larger material of children of this category—which have got tuberculosis in spite of BCG-vaccination—should be suitable as a foundation for a critical judgement of the duration of immunity following BCG-vaccination. This is, however, difficult, if not impossible owing to the following reasons (among others): It would take an absurdly long time to collect a material adequate for proper statistical analysis; the intensity of infection (Heimbeck 1952), and the sensitivity to tuberculin and immunity, respectively must be considered; furthermore, constitutional negative qualities can—as has been hinted at by the small material described below—possibly exist.

In this material of 3,112 BCG-vaccinated children, 7 of them have had clinically verified or suspected tuberculosis. The tuberculin reaction could not be used in this BCG-vaccinated material as a means of diagnosis as among the unvaccinated and objections can possibly be made that the figure may therefore be too low. These pupils have, however, from the health care viewpoint been well looked after and SR's, lung roentgen examinations, etc., have been taken in all uncertain conditions, which is why the author believes that the cases missed have been very few—even if they have not been completely excluded. Regarding superinfection and its related problems, the author has dealt with this in Chapter I and in Chapter VII. Two of these seven children showed clinical tuberculosis before school age.

b. Case histories

1. *G.J.* boy born 1939. 6 cases of tb. in family: mother E. N. 1939, hilar adenitis with +ve tb. in sputum 1940. Grandmother died from pulm. tb. 1922, aunt died from pulm. tb. 1930, grandfather died from pulm. tb. 1942. Another aunt with pulm. tb. 1911 lived at that time in the pat's. home. Aunt hilar adenitis 1942.—Pat. (*G.J.*) admitted 1940 to Samariten Children's Hosp. for eczema. BCG-vaccinated then with 0.2 ml. vaccine intracut. 13/3 1940 after that Mx 100 TU had been -ve. 24/4 1940 Mx 100 TU 12×16 mm. Under continuous control at Tb. Dispensary, inc. April, Oct., Dec. 1944 with normal lung roent. 18/11 1942 Patch test +ve. March 1945 diag: Prim. pulm. tb.—bilat. hil. pulm. tb. for which pat. admitted to Lovisas Children's Hosp. for one month. Mx. 100 TU 13×10 mm. Guinea pig inoc. or other bact. culture on stomach irrigation fluid not done. Lung cond. soon stationary and later regressed. Cont. control at Tb. Dispensary nothing of note. Mx 100 TU remained in the follow-up about 20×20 mm. Adolf Fredrik Elem. sch. the whole time. Father unemployed; family overcrowded.

2. A. W. boy born 1936. Father pulm.tb. Pat. BCG-vaccinated with 0.05 mg intracut. 12/10 1948 in sch. Dec. 1948 admitted Norrtull's Children's Hosp. for obs. high SR. Patch test +ve. Lung roent. normal. Jan. 1949 Patch test +ve. May 1950 Tb. Dispensary. Pulm.tb.? Bronchopneumonia? Not admitted. Tb. Dispensary control. 23/5 1950 Mx 5 TU 10×10 mm. Guinea pig inoc. or other bact. culture not done. Lung findings showed rapid retrogression. Cont. control at Tb. Dispensary—nothing of note. 4/2 1951 Mx 100 TU 15×25 mm. Hjorthagen's Elem. sch. the whole time; family crowded.
3. L. N. boy born 1939. Brother pulm.tb. 1948. Pat. BCG-vaccinated 14/4 1947 intracut. 0.10 mg. Sala Disp. 1/11 1947 Patch test +ve. 20/1 1948 Patch test +ve. Sept. 1948 E.N. Lung roent. then normal. SR high the whole time. Jan. 1949: Prim.tb. (in BCG-vacc. pat.). Admitted Norrtull's Children's Hosp. and Tjärnan Children's Sanat. Repeated Guinea pig inoec. on stomach irrigation fluid and other bact. cultures -ve. 15/12 1949 Patch test +ve. Slow regress of hilar changes, only complete after one year. Later control—nothing of note. 4/2 1951 Patch test +ve. Went to Engelbrekt's and Hjorthagen's Elem. schs. Family crowded.
4. R. J. boy born 1939. Father died from pulm.tb. 1945. Sister tb. glands. 1941. Pat. BCG-vaccinated intracut. April 1942. Sept. 1942 Mx 100 TU 12×15 mm. Sept. 1943 admitted Samariten Children's Hosp. for eczema. Then Mx 100 TU 18×14 mm. Tb. Dispensary control on account of the tb. environment. Dec. 1944 bilat. hilar adenitis. Admitted Samariten Hosp. and Tjärnan Sanat. Mx 100 TU +ve. Guinea pig inoc. and other bact. culture on stomach irrigation fluid not performed. Since 1946 once more control at Tb. Dispensary Roent. 1946: Calc. in rt. hilus + big left hilar shadow. 15/10 1946 Mx 100 TU +ve. 25/11 1947 Patch test +ve. Later control—nothing of note. Went to Maria and Söderbärke Elem. schs. Family had good space in their home.
5. L. H. girl born 1942. Father died from tb. 1941. 2 aunts died from tb., 2 other aunts have now healed pulm. tb. Grandmother and an aunt died from pulm. tb. An uncle with pulm. tb.—now healed. Pat (L. H.) vaccinated intracut. 15/8 1949 at Samariten Children's Hosp. 15/10 1949 Patch test +ve. 26/10 1949 Patch test +ve. 4/1 1950 fever and E.N., admitted Samariten under diagnosis: tb. infection (in BCG-vacc. pat.). Lung roent. normal. Repeated Guinea pig inoec. on stomach irrigation fluid -ve. Discharged free from clinical symptoms after one month. Later control—nothing of note. 10/2 1951 Patch test +ve. Maria Elem. sch. the whole time. Family had good space in their home.
6. B. A. boy born 1940. Grandfather died from intestinal tb. Mother E.N. 7 times 1940—48. Also exposure to tb. at another family during the summer 1948. Pat. Mx. -ve. 100 TU repeated occasions at Tb. Dispensary control. BCG-vaccinated intracut. there 25/10 1947. 28/1 1948 Mx 100 TU 22×30 mm. Lung roent. then normal. Oct. 1948 rt. hilar adenitis. admitted Norrtull's Children's Hosp: Bilat. pulm. tb. + E.N. Mx 5 TU 15×15 mm. Repeated Guinea pig inoec. on stomach irrigation fluid and other bact. cultures -ve. Later admitted Tjärnan Sanat. up to July 1949. Subsequent control at Tb. Dispensary—nothing of note. 28/11 1950 Patch test +ve. 6/2 1951 Mx 100 TU 25×25 mm. Went to Kungsholm's Hökarängen's. Gubbängens and Midsommarkransen's Elem. schs. Family overcrowded.
7. J.-E. H. boy born 1937. Father died from pulm. tb. 1946. Mother bilat. pulm. tb. 1947. Pat. BCG-vaccinated 23/8 1943 when the father's tb. was noticed. 26/11 1943 Mx 100 TU 20×17 mm. Lung roent. normal. Continued control at Tb. Dispensary—

nothing of note. 27/10 1945 Patch test +ve. 15/3 1948 Patch test +ve. 13/5 1949 Patch test -ve. 18/10 1949 Mx 5 TU 20×20 mm. Lung roent. showed suspected calcifications on the rt. side. Feb. 1950: In left 1st. intercostal space—soft opacity. Admitted Norrtull's Children's Hosp. for two months for pulm. tb. Patch test +ve. SR normal. Repeated Guinea pig inos. on stomach irrigation fluid and other bact. cultures -ve. Lung roent. changes were there considered to be stationary and old standing. Continued control at Tb. Dispensary regarding lung roent. status quo, and nothing of note in general. 3/2 1951 Patch test +ve. 7/3 1951 Mx 5 TU 11×12 mm., BCG-tuberculin 0.05 mg 25×25 mm. Went to Fredhäll's Kungsholm's and Midsommarkransen's Elem. schs. Family had good space in their home.

c. Discussion

Of these seven described cases two (Nos. 1 and 4) were taken ill prior to starting school. See further Tab. 28. All have had a great chance of contracting tuberculosis through near relatives; case 6, in addition, spent a summer in another tuberculous environment. Two cases showed an exceptionally marked family history of tuberculosis and in general it must be assumed that for these seven children there had been frequent and great exposures to tuberculosis. All of them have shown moderate tuberculin allergy at the post-vacc. control test: none has developed Koch's phenomenon. Four of the children have been BCG-vaccinated at school age, but only one of them directly through the school doctor. The intervals between the BCG-vaccination and the time of appearance of clinically verified tuberculosis in the seven cases have been (in months): 5, 12, 17, 19, 28, 60 and 74 respectively. As a rule several tuberculin tests have been performed between the BCG-vaccination and the actual diagnosis of clinical tuberculosis, and the interval between the last positive tuberculin test and the tuberculosis infection has been: 3, 4, 8, 9, 15, 16 and 27 months respectively. Whether tuberculin allergy has disappeared before the appearance of the clinical tuberculosis or not cannot be judged with certainty, but in no case has a negative tuberculin test been recorded between the BCG-vaccination and the time of the clinical infection. To judge from the hospital diagnosis, clinical primary tuberculosis has occurred in most cases (at least 4); two of these also had Erythema nodosum. In two other cases the clinical picture was that of slightly atypical primary tuberculosis, and one of these also had Erythema nodosum. In the last case (No. 2) it was, on the whole, doubtful whether it had been tuberculosis or unspecific bronchopneumonia. Because the school doctor treated this child as if he had a tuberculous superinfection — and this could not be excluded—this case was included here.

Some authors state that in order to diagnose human superinfection it

TABLE 28
Children with clinical tuberculosis who have been previously BCG-vaccinated.

Case history number	Tuberculous environment and exposure				BCG-vaccinated		Time interval:		Diagnosis	Bact. test (or cultures)	Note
	Father	Mother	Brothers or sisters	Others	Age in years	Post-vacc. tub. test	BCG-vaccination—diagnosed clin. tb.	Last pos. tub. test—diagnosed clin. tb.			
1.		+		+	7 12 Hosp.	Mx 100 TU 1x16 mm	Mths 60	Mths 27 Patch test pos.	Prim. pulm. tb.	not performed	tb. pri school
2.	+				12 Sch.	Neo-T pos.	19	16 Patch test pos	Pulm. tb. ? Bronchopn. ?	not performed	doubtful
3.			+		8 Disp.	Neo-T pos.	17	8 Neo-T pos.	E. N.+prim. pulm. tb.	neg	Psych. debil.
4.	+		+		3 Disp.	Mx 100 TU 12x15 mm	32	15 Mx 100 TU 18x14 mm	Prim. pulm. tb.	not performed	tb. pri school
5.	+			+	7 Hosp.	Patch test pos.	5	3 Patch test pos.	E. N.+tb. infect.	neg	
6.		+		+	7 Disp.	Mx 100 TU 22x39 mm	12	9 Mx 100 TU 22x30 mm	E. N.+ prim. pulm. tb.	neg.	
7.	+	+			6 Disp.	Mx 100 TU 20x17 mm	74	4 Patch test pos.	Pulm. tb.	neg	

is virtually necessary to demonstrate tubercle bacilli in the sputum or stomach irrigation fluid (Myers 1951, Alexandre 1952). I consider this requirement a little too strict because the clinical course in general can give as good a basis for the diagnosis e.g. elevation of the SR, fever, positive lung roentgen, drawn-out course, negative virus test, etc. In only four of these seven cases were bacteriological tests carried out and in none of these were tubercle bacilli demonstrated.

The ages at the onset of illness have been: two before the beginning of school (5 and 6 years of age), three in the younger school years (7,8 and 10 years), and two at puberty (13 and 14 years) when a more severe illness can be reckoned with. It can be further stated that the period of hospitalisation in cases 1, 3, 4, 6 and 7 was over six months, but did not

exceed one year. In the two others the healing was considerably more rapid. Regarding the long-term outlook—the follow-up time exceeded 5 years after tb. infect. in only two cases, and in the others was: 12, 13, 15, 26 and 28 months respectively, but in no case was a more malignant type of post primary tuberculous manifestation seen—and after a year all these children were able to return to school. Case 3 has subsequently got a primary chronic polyarthritis, but is free from tuberculous symptoms. Summing up, I have had an impression that the tuberculous infection has not had a malignant course in any of these seven cases, but on the contrary been rather mild and benign. This agrees with what was pointed out in the introduction that BCG-vaccinated children exhibit more benign types of tuberculosis than do other tuberculous patients.

Of all the 3,112 BCG-vaccinated school children, only seven have had a suspected or clinically verified tuberculosis infection—two of them before beginning school. Two of the other five were vaccinated before school age. All above-mentioned seven children belonged to families where one or more members suffered from open tuberculosis. In none of these seven cases have tubercle bacilli been demonstrated. The tuberculin test has been positive at an average time of at least one year before the onset of illness. The clinical types of tuberculosis found were benign.

C. Comparison between Tuberculosis Morbidity and Mortality in BCG-Vaccinated and Unvaccinated School Children

a. Social status and contact

As has been previously mentioned, the author has not got an objection-free control material at his disposal as in Scandinavia one has not considered it right to only BCG-vaccinate every other child—but one must vaccinate all who so wish. This method of getting a control material is, according to *Irvine* (1949) unsatisfactory, and *Levine and Sackett* (1946) also think that it is usually the more intelligent and co-operative parents who accept vaccination for their children. This is hardly so in the present material. The 843 non-vaccinated children—as is seen in Tab. 29—are similarly dispersed among the different social classes as are the vaccinated. As can be also seen in Fig. XVII, they also have nearly identical housing conditions.

Further, it has been found that of these 843 non-vaccinated children, 201 tuberc. neg. children are proved to be vaccination refusers and probab-

TABLE 29

Percentage division into social classes among vaccinated, non-vaccinated and vaccination refusers.

	Social classes		
	I %	II %	III %
Whole material	9.6	26.0	64.4
BCG-vaccinated	10.1	25.6	64.3
Non-vaccinated	7.7	27.5	64.8
Vaccination refusers	7.0	31.3	61.7

ly in the tuberculin positive category there are some who have previously been refusers, but it is, however, hard to prove this. The division of vaccination refusers into social classes is, in the main, the same as that of the total material (see page 55).

From the above it is clear that the non-vaccinated have a social status comparable with the vaccinated children and therefore a medical comparison is justified and *Levine* and *Sackett's* above-mentioned objections do not apply here. As has been shown in Ch. IV, the vaccinated and non-vaccinated children also have a similar division regarding sex and age. The small percentage difference given regarding the existence of a tuberculous environment between the groups (see page 52) ought to be partly explained by the more thorough observation made in cases of clinical tuberculosis.

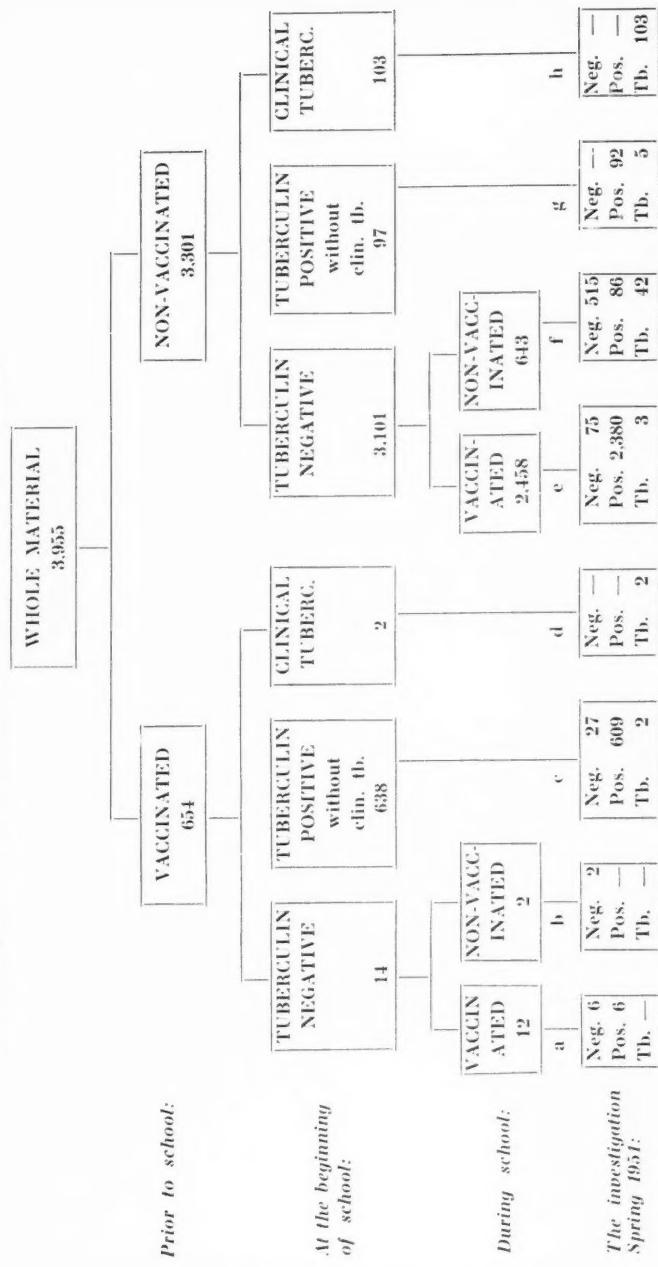
b. *Tuberculosis morbidity*

When comparing morbidity in non-vaccinated and vaccinated groups, it is essential that initially both are absolutely equivalent and comparable. Because the follow-up concerns, above all, the effect of BCG-vaccination carried out in the Elementary school, this comparison ought to be made between groups which have had the same starting conditions at 7 years of age.

Tab. 30 reveals the material, with this idea in mind, and it will be the basis for the further discussion. According to the above-mentioned, the most important comparison between vaccinated and non-vaccinated children will principally concern *e* and *f*, Tab. 30, which groups were non-vaccinated and tuberculin negative at the beginning of school.

TABLE 30

Survey regarding BCG-vaccination, tuberculin positivity and actual clinical or healed tuberculosis in the material; the state recorded before, at the beginning of, and during school and in connection with the end of this follow-up.



Comparison can also be made from other—and in my opinion—less important viewpoints. Thus, all the vaccinated ($a+b+c+d+e$) can be compared with all the non-vaccinated ($f+g+h$). In the same way one can compare vaccinated children, positive or negative, who have not presented signs of clinical tuberculosis before school age ($a+b+c+e$) with equivalent groups among non-vaccinated children ($f+g$). It is, however, essential that in all comparisons inverters without signs of clinical tuberculosis are excluded as tb. cases, because if these occur among those previously BCG-vaccinated—they go undiagnosed.

At a closer examination of the material from the above-mentioned viewpoint it appears, as is seen from Tab. 31, that 177.9 % of the non-vaccinated children have had symptoms of clinical tuberculosis; at the same time there was only 2.25 % of such cases among the successfully BCG-vaccinated children. This ratio is 1:79 in favour of the vaccinated, and the protection of those vaccinated is 99 per cent.

As the actual date of vaccination for some of the children vaccinated before school is not known—the observation years cannot be given for these groups.

If, instead, children of both groups having had symptoms of clinical tuberculosis before school age are excluded, it is found that in the subsequent course clinical tuberculosis occurs in 1.61 % of the vaccinated and 63.5 % of the non-vaccinated school children. This ratio is 1:39, and the protection of those vaccinated is 97 per cent.

Here also is given the number of person/years of observation during school: the observation time for those tuberculin negative and vaccinated at school has, however, been counted from the actual date of vaccination. Because of this, the mean observation time is less for those vaccinated as this, in some cases, has been first performed one or two years after the beginning of school. The clinical tuberculosis rate in vaccinated and non-vaccinated children with regard to the observation years is found to be 1:33 and the protection of those vaccinated to be, here too, 97 per cent.

In this connection the most valuable comparison from a scientific viewpoint is the following: Among the children BCG-vaccinated in school who earlier were tuberculin negative, 1.22 % have acquired symptoms of clinical tuberculosis, but among those tuberculin negative at the beginning of school who were not BCG-vaccinated, 65.3 % have developed symptoms of clinical tuberculosis. This ratio vaccinated/non-vaccinated is 1:54 and the protection of those vaccinated is 98 per cent. This difference is of the highest statistical significance.

If counted from the number of person/years of observation during

TABLE 31

Comparison between morbidity in clinical tuberculosis in BCG-vaccinated and non-vaccinated children according to different bases of judgement. (Group division according to Tab. 30.) (All successfully vaccinated at post-vacc. tuberculin test; re-vaccinations not specially registered.)

	School group				Total material					
	N	S			Number TB cases	Number TB cases	Number TB cases	Average period observed years	Person/years observed	Rate per 1,000 person-years observation
Clinical tuberculosis among:										
All vaccinated groups (a+b+c+d+e)	1	0.54	6	4.72	7	2.25		—	—	—
All non-vaccinated groups (f+g+h)	62	138.4	88	222.8	150	177.9		—	—	—
All vaccinated with exception of those vacc. who had clin. tb. before school age (groups a+b+c+e)	0	0	5	3.94	5	1.61	3.7	11.519 ^a	0.43	
All non-vaccinated with exception of those non-vacc. who had clin. tb. before school age (groups f+g)	16	39.8	31	91.7	47	63.5	4.4	3,229 ^b	14.3	
All vaccinated in school group (e)	0	0	3	2.80	3	1.22	4.0	9,804 ^c	0.31	
All non-vaccinated, tub. neg. at the beginning of school (group f)	13	37.5	29	98.0	42	65.3	4.4	2,830 ^b	14.8	

a = From beginning of school, and if not then vaccinated, from actual vaccination date.

b = From beginning of school.

c = From actual vaccination date.

school (for the vaccinated the time is counted from the date of vaccination) the rate of clinical tuberculosis per 1,000 person/years of observation (Tab. 31) will be 0.31 for the vaccinated and 14.8 among the unvaccinated.

The ratio vaccinated/non-vaccinated is 1:48 and the protection of those vaccinated is 98 per cent.

c. Tuberculosis mortality

No deaths from tuberculosis have occurred in any of the groups—i.e. vaccinated or non-vaccinated; so such a comparison is impossible.

d. Fulfilment of Park's standard requirements

This investigation's possibility to fulfil Park's requirements as stated on page 18 is good concerning points 1, 2, 3b, c, d and e, 4 and 5. Point 6 is not valid as no death occurred. Furthermore, I refer the reader regarding morbidity comparison to what has already been stated on page 19. The selection by alternation (point 3a) has not been carried out for earlier-mentioned reasons which have been adequately discussed. The author, therefore, is of the opinion that his material—with the exception of these unavoidable factors—is well up to the requirements that can possibly be demanded.

CHAPTER VII

Tuberculin Allergy Following BCG-Vaccination

A. Different Types of Tuberculin

The theoretical bases for tuberculin testing and the relationships between tuberculin allergy and acquired immunity against tuberculosis have been given in Chapter I. Tuberculin allergy can be tested in many different ways and the result must, to a great extent, depend on the method used (Ustvedt 1950). I refer the reader to *Silverstolpe & Östhholm* (1954) concerning the different types of percutaneous methods. These authors give an account of the development and composition of the ointments which have been produced by SBL, and which have been used during this investigation.

The total percentage of those who are tuberculin positive in a material will be, however, largely dependent on what strength is used in the intracutaneous tuberculin test (according to Mantoux). In this investigation Mantoux 100 TU (1 mg OT) has been used as the last test. Other authors have gone further—up to 300 TU (3 mg) and even higher; but in my opinion Mantoux 100 TU is completely adequate as a final test in an investigation with the present aims. Further, this dose has for a long time been used as the final test in Stockholm's Elementary schools and has the practical advantage that one can be satisfied with one percutaneous test and only one following intracutaneous test; I have, therefore, used this method exclusively. The tuberculin for tuberculin ointment (SBL) and the Mantoux test (SBL) has been prepared from both human and bovine strains of tubercle bacilli (Silverstolpe 1954).

Ustvedt (1950) points out that the slightest degree of sensitivity is that which can only be detected by the use of the tubercle bacillus (Koch's phenomenon—diagnostic BCG-reaction). The next step may be the sensitivity to BCG-tuberculin and then the slight sensitivity to the most sensitive tuberculin test. Theoretically, it can be thought, that the tuberculin test following BCG-vaccination can give a higher percentage of tuberculin positive individuals if testing is carried out with a tuberculin

produced from the same strain as the BCG-vaccine (Lind & Holm 1943, Rinvik 1944, Magnusson & Lithander 1949, Wilken—Jensen 1952).

Together with *Silverstolpe* the author has made a trial (unpublished) with such a BCG-ointment whereby BCG-vaccinated school children had more definite reactions than with tuberculin ointment SBL. There was, however, no statistically significant difference in the results of these Patch tests. These results of ours seem to be in agreement with those described by *Wilken—Jensen* (1952). It must be further noted that the procedure of preparing BCG-ointment and BCG-tuberculin for intracutaneous use usually differs from that of Old-tuberculin and PPD-tuberculin. The former is not heat-treated to the same extent which makes a direct comparison of the results uncertain.

From their investigations *Lind & Holm* (1943) concluded: "There is no reason, on account of the studies reported (here), to deviate from the practice hitherto employed in Denmark, which requires that if a BCG-vaccination is to be recognised as effective the vaccinated subject must show an unquestionable positive reaction to the ordinary tuberculin produced by a virulent strain."

It is thus seen that from both a practical and a scientific viewpoint it is desirable in the investigation of the efficacy of BCG-vaccination to obtain a definite sensitivity to ordinary tuberculin produced from human strains (Ustvedt 1952, Kleinschmidt 1953). As this procedure has been in continuous use in the health control in Stockholm's Elementary schools the author has not diverged from it. Further, a different procedure should make a general comparison more difficult.

B. Inversion and Complications Following BCG-Vaccination

The time of inversion and the percentage of tuberculin positive persons at the post-vaccination control test have been outside the scope of this investigation and the author has not gone into this question. These problems have, as in the case of Stockholm's Elementary schools, formerly been written about by *Hjärne* (1946). The total tuberculin positive individuals at the post-vaccination control test in this (*Hjärne's*) investigation during 1945—46 has been about 95 per cent using a Mantoux test up to 100 TU, which is in good agreement with other Scandinavian authors using intracutaneous vaccination. The readers are also referred to *Hjärne* (1946) concerning the local reactions and complications of vaccination which is outside this thesis.

TABLE 32
Survey of the tuberculin reaction of BCG-vaccinated children at the end of the observation time. Reverters inserted where the first negative tuberculin reaction occurred.

Years after BCG-vacc.	0 ₁	1 ₂	1 ₃	2 ₁	2 ₂	3 ₁	3 ₂ - 4 ₁	4 ₁	5 ₁	5 ₂	6 ₁	6 ₁ - 7 ₁	7 ₁	8 ₁	8 ₂	9 ₁	9 ₁ and more	Total number		
Tub. react.	+	+	+	+	-	+	-	+	-	+	-	+	-	+	-	+	-	+		
N	Adolf Fr.	2	1	21	2	143	3	167	1	90	1	88	3	24	0	22	0	16	0	85
Engelbrekt	0	3	55	4	45	2	92	4	53	3	57	3	48	0	18	1	16	0	11	
Fredhäll	0	0	5	0	195	5	17	0	89	2	82	1	50	1	26	0	17	0	20	
Essingen	0	1	6	0	126	1	5	0	56	2	41	0	29	0	5	0	2	1	11	
Schoolet	Number	2	5	87	6	509	11	281	5	288	8	268	7	151	1	71	1	51	2	277
% tub. neg.			6.5		2.1		1.7		2.7		2.5		0.7		1.4		3.8		2.6	
S	Hjorthagen	0	1	4	0	77	6	14	3	33	0	47	0	17	0	3	0	4	0	10
Maria	1	0	181	10	88	4	21	4	121	6	97	3	36	3	24	2	15	0	32	
Mids.kr.	1	0	169	6	64	5	14	4	64	3	31	1	18	1	11	1	9	0	21	
Schoolet	Number	2	1	354	16	229	15	49	11	218	9	175	4	71	4	38	3	28	0	1708
% tub. neg.			4.3		6.1		18.3		4.0		2.2		5.3		7.3		0		63	
Total number	4	6	441	22	738	26	330	16	506	17	443	11	222	5	109	4	79	2	505	
% tub. neg.			4.8		3.4		4.6		3.3		2.4		2.2		3.5		2.5		3.5	

C. The Duration of Tuberculin Allergy in Different Year-Groups BCG-Vaccinated before School Age and in School

a. Introduction

The duration of post-vaccinal tuberculin allergy plays a big part in the estimation of the period of acquired relative protection, and in connection with this—the question of additional testing and re-vaccination. One ought to strive for as long a post-vaccinal tuberculin allergy as possible. As previously mentioned, the post-vaccinal tuberculin allergy in several BCG-vaccination surveys has been quoted as short—“the tuberculin reaction is usually negative after four years” (see page 18). It is seen from Tab. 1, however, that this is not wholly correct, but is a considerable underestimation in the case of intracutaneous vaccination.

Tab. 32 has been made in order to throw further light on the state of tuberculin allergy within the material, even in more detail than in Chapter IV. This reveals the tuberculin reaction in all the BCG-vaccinated—and even the re-vaccinated—at the end of the observation period, Spring 1951. Reverters are there inserted at that time that the first negative tuberculin reaction was noticed and thereafter left out. Therefore this Tab. 32 does not give any correct information in figures about the development of post-vaccinal tuberculin allergy in groups of school children who were vaccinated at the same time and then followed-up continuously.

On the other hand, the material given in Tab. 32 has been used as a basis for an estimation of the annual reversion rate during the first nine years following a successful BCG-vaccination. It is then seen (Tab. 33) that this post-vaccinal change from a positive to negative tuberculin reaction is fairly constant during these years and is about 1 per cent annually. It is noteworthy that it is no bigger during the first years following vaccination. During the last period, 9–10 years after vaccination, the number of children under observation was small and the author has not considered himself entitled to draw any conclusions from them. Fig. XVIII illustrates the remaining number of tuberculin positive individuals during the first 9–10 years following vaccination, and it is founded on the information given in Tab. 33.

In order to follow the development of tuberculin allergy an annual and complete tuberculin testing ought to be carried out. The effect of such repeated tests on the body is not certain, but the possibility of a desensitisation against tuberculin has been earlier suggested (Rosemberg 1951), and possibly the result of, for instance, *Groth-Petersen* (1949).

TABLE 33

Estimation of reversion risk following successful BCG-vaccination. Tab. 32 as basis; where all observations are supposed to have been carried out in the middle of the respective periods. The risks are calculated for periods of complete years, starting from time of vaccination.

Period	No. of observations during period	No. of revertors during period	% risk	% annual risk	% still tuberculin pos. at end of period
0 - 1.4	3,112	6	0.19	0.76	99.8
1.4 - 1	3,102	22	0.71	0.95	99.1
1 - 2	2,639	26	0.98	0.98	98.1
2 - 3	1,875	16	0.85	0.85	97.3
3 - 4	1,529	17	1.11	1.11	96.2
4 - 5	1,006	11	1.09	1.09	95.2
5 - 6	552	5	0.91	0.91	94.3
6 - 7	325	4	1.23	1.23	93.1
7 - 8	212	2	0.94	0.94	92.2
8 - 9	131	1	0.76	0.76	91.6
9 - 10	58	0	0	0	(91.6)

might be referable (see page 18) to a partial desensitisation caused by frequent tuberculin controls (compare Birkhaug's "iathergi").

Most children in this material have—in addition to the repeated tuberculin test given on page 22—also been tuberculin tested during the years 1948, 1950 and 1951. Thus, for most of the children an annual tuberculin test of up to Mantoux 100 TU has been performed. I have primarily followed those groups where BCG-vaccination has been done to a greater extent during the spring- and autumn terms 1945, the spring term 1947 and the spring- and autumn terms 1948 (see Fig. XV), so as to get groups which are in agreement regarding the age at vaccination, the vaccine used and the duration of follow-up.

b. Division into groups

In accordance with the above-mentioned, the author has constructed the following groups:

- Group 1. BCG-vaccinated 1943 or earlier (1939 up to 30/9 1943); total 217 pupils, then at the age of 0—7 years.
- Group 2. BCG-vaccinated 1944 (1/10 1943—30/9 1944); total 111 pupils, then at the age of 2—8 years.
- Group 3a. BCG-vaccinated 1945 (1/10 1944—30/9 1945); total 262 pupils, then at the age of 3—9 years.

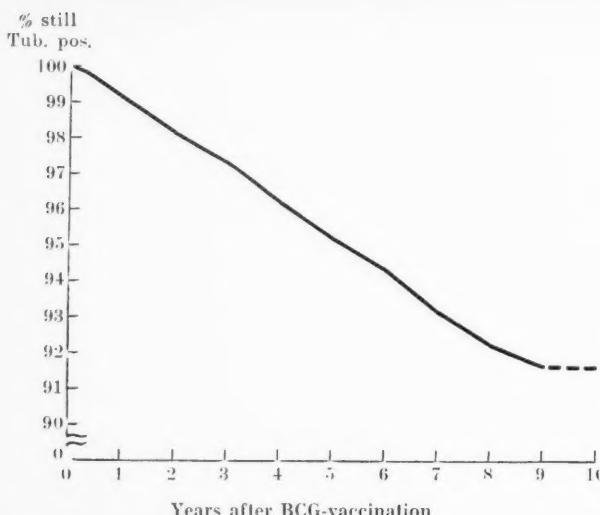


Fig. XVIII. Percentage children with persisting positive tuberculin reaction the years following successful BCG-vaccination.

- Group 3b. BCG-vaccinated *in school 1945* (1/10 1944—30/9 1945); total 157 pupils, then at the age of 7—9 years.
- Group 4a. BCG-vaccinated *1946* (1/10 1945—30/9 1946); total 461 pupils, then at the age of 3—10 years.
- Group 4b. BCG-vaccinated *in school 1946* (1/10 1945—30/9 1946); total 355 pupils, then at the age of 7—10 years.
- Group 5a. BCG-vaccinated *1947* (1/10 1946—30/9 1947); total 528 pupils, then at the age of 3—9 years.
- Group 5b. BCG-vaccinated *in school 1947* (1/10 1946—30/9 1947); total 427 pupils, then at the age of 7—9 years.
- Group 6a. BCG-vaccinated *1948* (1/10 1947—30/9 1948); total 328 pupils, then at the age of 3—11 years.
- Group 6b. BCG-vaccinated *in school 1948* (1/10 1947—30/9 1948); total 265 pupils, then at the age of 7—11 years.

All these children have been successfully BCG-vaccinated i.e. with positive post-vaccination tuberculin test. In exceptional cases there was no information about the intensity and size of this positive reaction, and for practical reasons the author has, in these cases, given the result of the nearest following tuberculin test, usually done 1 to 2 years later. If the tuberculin test has not been performed during a year, the child has been registered according to the previous year's tuberculin test. Reverters,

TABLE 34

Information about the environment (suspected or certain tuberculous exposure) in the vaccination groups.

Group	1	2	3a	3b	4a	4b	5a	5b	6a	6b
Per cent tuberculous environment in all children of the groups.	43.8	25.2	19.1	12.1	10.8	9.0	10.6	9.8	8.5	5.7
Tuberculous environment among reverters in relation to the total number of reverters.	1/9	1/7	2/20	2/13	2/19	0/13	0/33	0/23	2/11	1/7

even if later re-vaccinated, have subsequently been noted as negative (those showing short anergy are not included).

Groups 1 and 2 were thus all BCG-vaccinated prior to school; a-groups consist of those vaccinated both in and outside school, and b-groups were all vaccinated within the school's organisation.

c. *Tuberculous environment within the groups*

Besides being vaccinated through the kindergarten, day homes and private practitioners, groups 1 and 2 have partly been vaccinated through the "dispensär's" organisation, which means that a tuberculous environment has often been the cause of this measure. It is therefore of essential interest to scrutinise the information about the occurrence of a tuberculous environment or the suspicion of this within the different groups—see Tab. 34.

It is clearly seen from this table that the frequency of a tuberculous environment is much higher in the earlier age groups—especially in those vaccinated prior to school—and there are reasons to expect that this might influence the duration of tuberculin allergy. It is in group 3b that one first comes down to a frequency of tuberculous environment representative for the BCG-group of the whole material—see Tab. 14. The occurrence

of a tuberculous environment—as stated by nursing sisters, parents, etc.—in reverters is small and fairly constant. In such a case there are two possibilities:—either the quoted risk of exposure has been completely eliminated, or the child has, through natural or latent acquired immunity, conquered the re-infection and by this remained tuberculin negative (compare page 86).

d. Vaccination prior to school age; years 1939—44

In Fig. XIX is seen the decline of tuberculin allergy in group 1, i.e. children successfully vaccinated before school age up to 1/10 1943. In this and similar diagrams (for the other groups) that follow, the percentage division of the groups' annual tuberculin state is shown as a column one centimeter wide. The vaccination has in this group, to a large extent, been performed according to the prevailing principle of the 1930's, i.e. to usually reserve BCG-inoculation for people in a tuberculous environment, which is seen in Tab. 34. Possibly this is one factor causing the low percentage total reverters (4 %) and that in general there was such a resistant tuberculin allergy that a positive Patch test remained in 70 per cent, in spite of the fact that a large number of these children were of the age of puberty (23 per cent between 12 and 16 years). A positive tuberculin test up to Mantoux 100 TU has thus remained in 96 per cent of the children 8 years following vaccination.

The changing of the tuberculin allergy in group 2, i.e. children vaccinated in 1944 (1/10 1943—30/9 1944) is shown in Fig. XX. The numerical relation of this decline within the different groups is also made clear in Tab. 35. The frequency of a tuberculous environment is here, in group 2, rather less—25.2 per cent, but still high. The positive tuberculin tests have persisted to a somewhat less degree than in the previous group 1, but under all conditions the results of the vaccination are very satisfactory, as the reverters amounted to 6 per cent and the children with positive Patch test to 56 per cent.

e. Those vaccinated prior to school or through the school medical organisation; years 1944—48

The reader is referred to Tab. 35 regarding the numerical relations of the groups accounted for below (as those under d.). Percentage figures are shown graphically. Fig. XXI thus graphically shows the decline of tuberculin allergy in group 3a—children 3 to 9 years old, successfully vaccinated in 1945 (1/10 1944—30/9 1945). Of these children, furthermore, the conditions of those vaccinated through the school medical

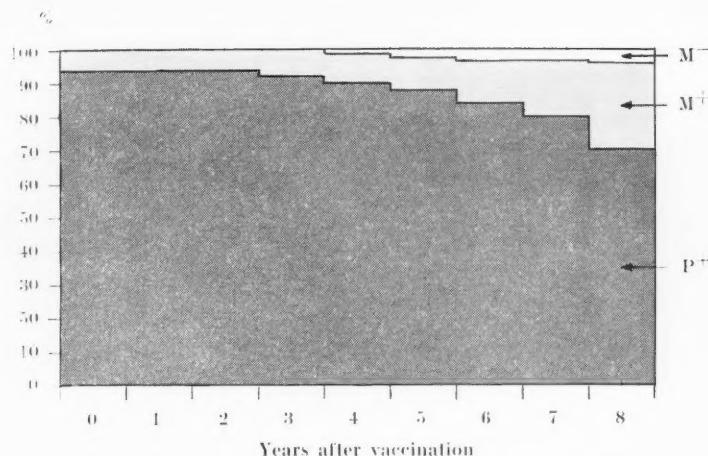


Fig. XIX. Decline of allergy in Group 1. 217 children successfully BCG-vaccinated prior to school—up to 1/10 1943.

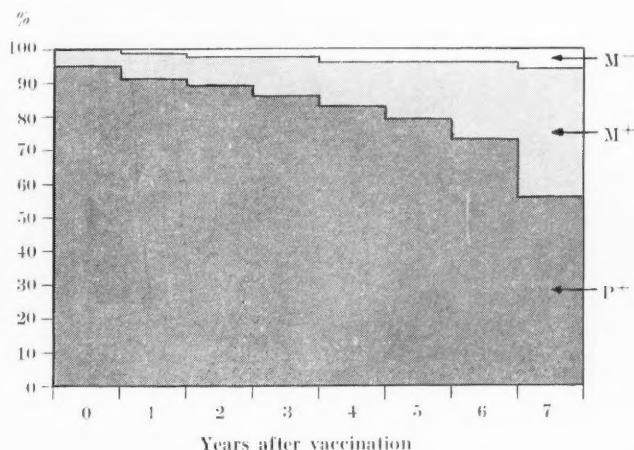


Fig. XX. Decline of allergy in Group 2. 111 children successfully BCG-vaccinated prior to school, 1/10 1943—30/9 1944.

organisation at the age of 7 to 9 have been separately shown in Fig. XXII. The total group contains 8 per cent revertors and 59 per cent still positive to the Patch test 6 years following vaccination, while on the other hand, the equivalent percentage figures for those of the total vaccinated at school

TABLE 35
The duration of tuberculin allergy in different age groups.
The state at follow-up control at different time intervals after vaccination.

Years after vace.		0	$\frac{1}{2}$	$\frac{1}{2} - \frac{1}{3}$	$\frac{1}{2} - \frac{2}{3}$	$\frac{2}{3} - \frac{3}{4}$	$\frac{3}{4} - \frac{4}{5}$	$\frac{4}{5} - \frac{5}{6}$	$\frac{5}{6} - \frac{6}{7}$	$\frac{6}{7} - \frac{7}{8}$	$\frac{7}{8} - \frac{8}{9}$						
Tab.	reaction	P ⁺	M ⁺	M ⁻	P ⁺	M ⁺	M ⁻	P ⁺	M ⁺	M ⁻	P ⁺	M ⁺	M ⁻	P ⁺	M ⁺	M ⁻	
(Gp I) No.	205	12	0	204	13	0	203	13	1	199	17	1	196	19	2	190	22
(Gp II) No.	106	5	0	101	9	1	99	10	2	96	13	2	92	15	4	88	19
(Gp IIIa) No.	217	45	0	204	55	3	195	58	9	189	60	13	186	62	14	175	71
(Gp IIIb) No.	116	41	0	110	47	0	103	49	5	98	50	9	96	52	9	91	56
(Gp IVa) No.	448	13	0	432	28	1	416	39	6	392	60	9	360	90	11	271	171
(Gp IVb) No.	346	9	0	334	21	0	324	27	4	302	47	6	280	68	7	219	123
(Gp V) No.	512	16	0	490	32	6	468	45	15	427	81	20	295	200	33		
(Gp VIa) No.	412	15	0	396	28	10	379	38	10	349	65	13	338	166	23		
(Gp VIb) No.	313	15	0	289	37	2	242	81	5	170	147	11					
(Gp VIIa) No.	253	12	0	235	30	0	197	65	3	135	123	7					

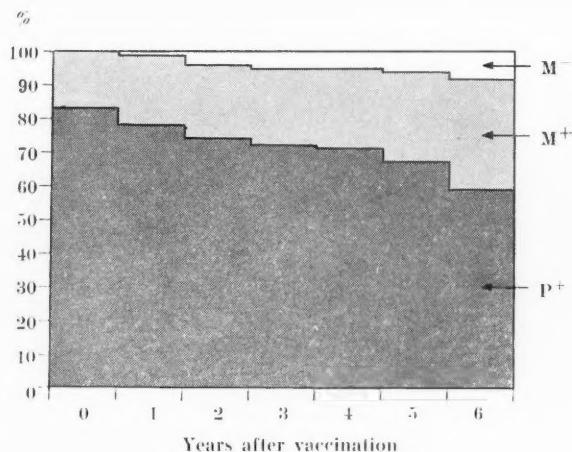


Fig. XXI. Decline of allergy in Group 3 a. 262 children successfully BCG-vaccinated prior to, and in school, 1/10 1944—30/9 1945.

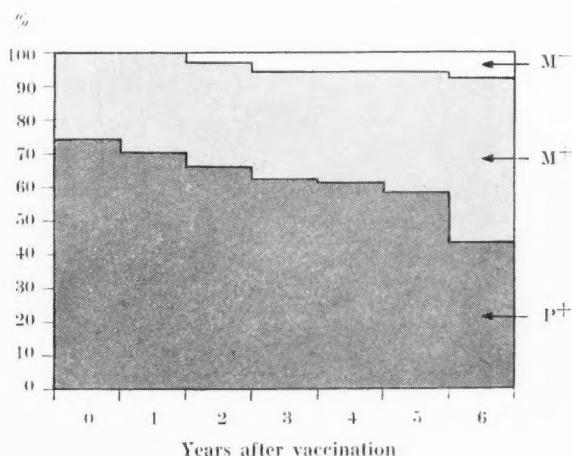


Fig. XXII. Decline of allergy in Group 3 b. 157 children successfully BCG-vaccinated in school, 1/10 1944—30/9 1945.

are 8 per cent and 43 per cent respectively. That there are fewer positive Patch test individuals in the latter group can possibly be connected with the fact that these children are older, but this does not agree with what was seen in group 1. This fact in connection with the greater number of

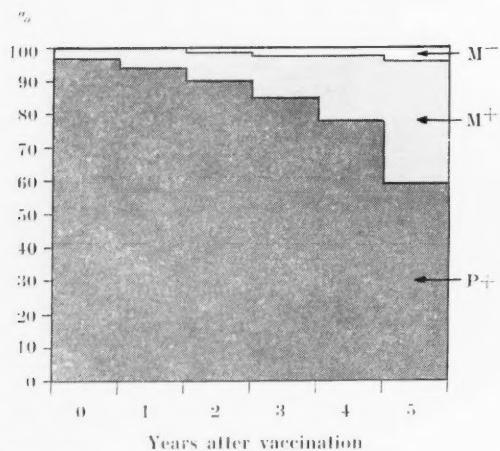


Fig. XXIII. Decline of allergy in Group 4 a. 461 children successfully BC_G-vaccinated prior to, and in school 1/10 1945—30/9 1946.

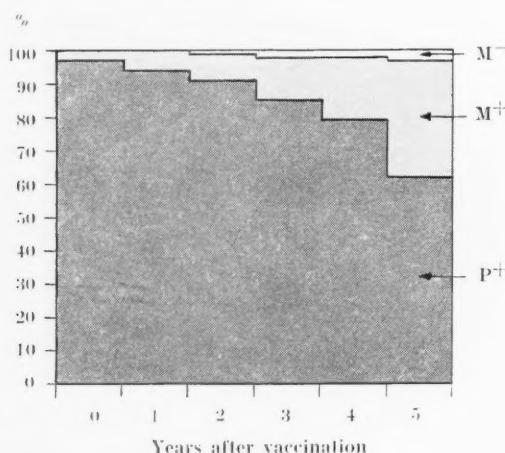


Fig. XXIV. Decline of allergy in Group 4 b. 355 children successfully BC_G-vaccinated in school 1/10 1945—30/9 1946.

reverters could even be thought to be connected with the vaccine used—that during Spring 1945 it was less active. This assumption is supported by the fact that in this group there were initially percentally considerably more negative Patch tests but Mantoux positive 100 TU (M⁺) at the post-

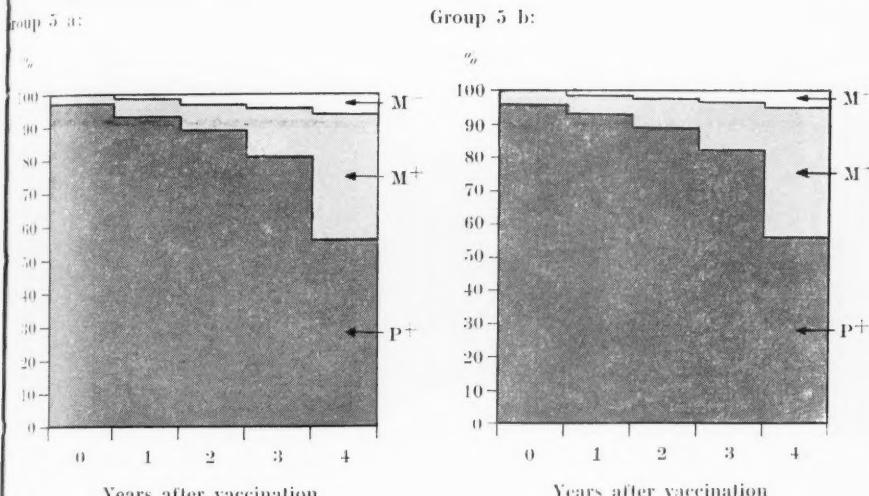


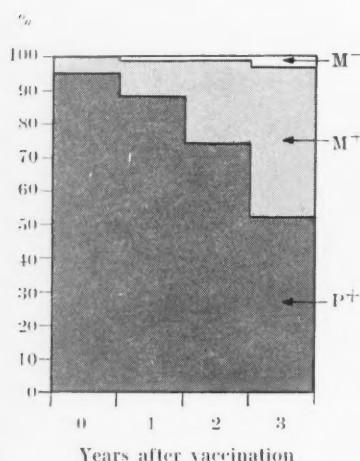
Fig. XXV. Decline of allergy in Groups 5 a and b. Successfully BCG-vaccinated 1/10 1946—30/9 1947. a, 528 children prior to, and in school, b, 427 children in school.

vaccination control test. Vaccination technique and dosage have been the same in all the groups.

Figures XXIII and XXIV show for groups 4a and b the decline of tuberculin allergy in children vaccinated during 1946 (1/10 1945—30/9 1946). The latter figure shows graphically the relationships in children vaccinated through the school's organisation at the ages of 7—10. The diminution in the tuberculin allergy is percentally less than in the above-mentioned groups 3a and b, but on the other hand the observation time is one year less. There were 4 per cent of reverters within the whole group and 3 per cent in the school-vaccinated group. There were 3 per cent more positive Patch test individuals, i.e. 62 per cent in the school vaccinated group (3b) in spite of their higher ages. Figure XXV shows the tuberculin allergy's decline for groups 5a and b, i.e. those vaccinated in 1947 (1/10 1946—30/9 1947); as before, those successfully vaccinated by the school medical organisation have been extracted and shown separately.

The decline is similar in both the groups, and the total number of reverters relatively insignificant, 6 per cent for a and 5 per cent for b. It is quite apparent that the decline of the percentage Patch test positives has increased more during the last investigation year—a feature hinted at.

Group 6 a:



Group 6 b:

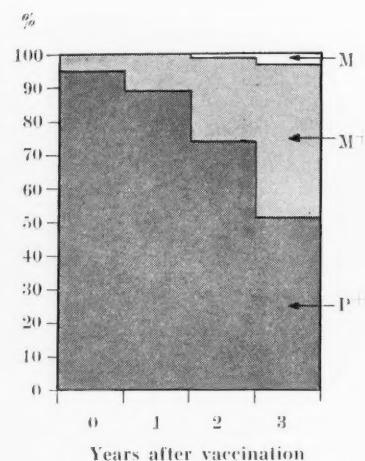


Fig. XXVI. Decline of allergy in Groups 6 a and b. Successfully BCG-vaccinated 1/10 1947—30/9 1948. a. 328 children prior to, and in school. b. 265 children in school.

if not so marked, in the earlier groups too. This might have its explanation in the partial desensitisation (see page 86) or might it be the result of increasing age?

Groups 6a and b are shown in Fig. XXVI; there the decline in tuberculin allergy is, in the main, similar to the previous groups and does not require any further comment.

f. Discussion

The decline of tuberculin sensitivity during the passage of years is gradual and moderate for all the groups; the total number of revertors varies from the lowest figure of 0.5 per cent annually in group 1 up to 1.5 per cent annually in group 5a. This implies that in a similar material one can reckon that after ten years 5—15 per cent of previously tuberculin positive persons will become Mantoux negative 100 TU, and this agrees well with the results shown in Tab. 33.

That decline in tuberculin sensitivity which is demonstrated on the cessation of a positive Patch test (P^+)—but with the Mantoux test 100 TU still positive (M^+)—is considerably more variable between the different vaccination groups. If one excludes the initially Patch test negative

TABLE 36

Annual decline of tuberculin sensitivity from earlier Patch test positive children (P^+) to positive only to Mantoux 100 TU (M^+) within the different vaccination groups.

Group	1	2	3a	3b	4a	4b	5a	5b	6a	6b
Observation years	8	7	6	6	5	5	4	4	3	3
% annual decline(P^+ to M^+)	2.5	4.7	2.7	3.7	6.8	6.4	8.8	8.8	13.3	13.7

persons with a positive Mantoux 100 TU (M^+), the annual diminution of the Patch test positive persons varies from 2.5 per cent in group 1 to a highest value of 13.7 per cent in group 6b—see Tab. 36.

Any important conclusions can by no means be drawn from this table, as so many factors can be thought to affect the decline—the vaccine, the frequency of the tuberculin tests and in some way even the age distribution within the group—even if the variations of these are small. What has been defined as human superinfection can again come into the picture, and one cannot avoid comparing this table (36) with Tab. 34, which shows the frequency of a tuberculous environment in the different groups. It is suggested that a greater possibility for superinfection causes a lower percentage of changing over from Patch test positive to a tuberculin allergy of a lower grade. Finally, the decline seen in Tab. 36 must also be evaluated against the background of the continued general decrease of tuberculosis morbidity and mortality in Stockholm.

D. Re-Vaccinated School Children

One cannot still with certainty know if a quickly disappearing post-vaccinal tuberculin positivity can be interpreted as a sign of constitutional factors, i.e. a relatively high natural resistance, or its opposite (Wallgren 1952). Bluhm (1948) believes that a considerable resistance occurs in these cases, while on the other hand Ustvedt (1951) supposes that these subjects contract tuberculous disease more often than those remaining tuberculin positive. The vaccine, vaccination technique, and the tuberculin test technique itself (used at the first vaccination) are factors which may

TABLE 37

Re-vaccinated, not including those not having successful primary vaccination nor those vaccinated during last term of follow-up (Spring 1951).

Year	0 - 1½	1½ - 2½	2½ - 3½	3½ - 4½	4½ - 5½	5½ - 6½	6½ - 7½	7½ - 8½	Total
Duration of tub. pos. after the prim. vacc. (latest known pos. tub. react.)									
Number of cases.	29	8	5	3	4	0	0	0	49
Time interval be- tween the vacc.									
Number of cases.	5	11	6	13	4	6	3	1	49

affect the sensitivity. The conceptions of latent tuberculin allergy and latent immunity respectively have been mentioned in the introductory Chapter I, and in this connection one can call attention to the accelerated local reaction at re-vaccination, the so-called "depth reaction" (Rinvik 1944) and that allergy after re-vaccination may appear after a shorter period of latency (Willis 1928).

Those BCG-vaccinated school children who did not have a positive tuberculin control test have not been included in this work.

Of the reverters of this material there were 49 successfully BCG-vaccinated school children who after their reversion were re-vaccinated. This is certainly a small number, but even so of interest for study. If there is a clear local reaction on the vaccination site it is not necessary to re-vaccinate more than once (Wallgren 1945). This has also been the rule in Stockholm's Elementary schools.

From Tab. 37 it can be seen that the tuberculin sensitivity in most of these 49 cases only existed for a short time—up to 1 1/2 years—and that re-vaccination was performed after very varying intervals. It can be further seen from Tab. 38 that the percentage of those re-vaccinated out of the total BCG-vaccinated children was only 1.57 per cent and that the duration of tuberculin allergy for this category was rather similar in both the school groups and for the whole material—average 1.9 years. These children have been re-vaccinated at an average interval of 3.7 years from the first vaccination—and even here it is very similar in both the school groups. The second vaccination resulted in a renewed hypersensitivity to

TABLE 38

Re-vaccinated, not including those not having successful primary vaccination nor those vaccinated during last term of follow-up (Spring 1951).

School	Re-vaccinated		Duration of tub. pos. after the prim. vacc. Average years	Re-vacc. after average years	Result of Re-vacc.	
	Number	% of total BCG-vacc.			Tub. neg	Tub. pos.
School group N	21	1.14	1.7	3.9	4	17
Adolf Fredrik	3	0.49	1.3	3.0	0	3
Engelbrekt	14	3.27	1.9	4.5	4	10
Fredhäll	1	0.19	1.0	2.0	0	1
Essingen	3	1.06	1.3	2.3	0	3
School group S	28	2.20	2.0	3.6	2	26
Hjorthagen	12	5.50	1.3	3.5	0	12
Maria	15	2.36	2.4	3.8	2	13
Midsommarkransen	1	0.24	1.0	2.0	0	1
Total	49	1.57	1.9	3.7	6	43

Patch test or Mantoux 100 TU in 43 of these 49 cases—but the duration of this is not known. There were no cases of clinical tuberculosis among this category.

E. Possibilities of Superinfection

In this connection one ought to comment on the possibilities of superinfection within the material, while, as has been pointed out in Chapter I, this can be supposed to have a direct connection with the duration of post-vaccinal tuberculin allergy. As was also emphasised in Chapter I, the frequency of superinfection is, to some extent, related to the general infection risk for tuberculosis for the age groups concerned in a community.

Bovine tuberculosis is now so extremely rare in Stockholm that it is not necessary to give it any practical consideration in this connection.

From two different statistics referred to in Chapter II, the annual tuberculosis infection risk at school age in Stockholm is estimated at 1 per cent and 4 per cent respectively. The former figure is—for previously stated reasons—too low, and the latter estimation is based on a somewhat

selected material. If one takes the average and estimates the annual risk as 2.5 per cent, then the total risk during the school period concerned (7—15 years) will be 20 per cent. If one is pessimistic and takes the 4 per cent figure, then the total risk for the same school period would be 32 per cent.

There are no grounds whatever for the supposition that this risk should be bigger in the BCG-vaccinated school children than for the non-vaccinated ones in the above-mentioned statistics, especially as in my material, (according to Ch. IV) the BCG-vaccinated children have had a statistically verified lower frequency of tuberculous environment than the non-BCG-vaccinated including those spontaneously positive.

I have not had the possibility, as Hertzberg (1948), to—with the aid of an increased tuberculin sensitivity—try to estimate in which cases superinfection occurred among the BCG-vaccinated children. On the whole, the author is doubtful about this possibility—as other factors which interfere with the fluctuations of allergy can be difficult to exclude. In any case, the moderate infection risk that exists during the school years cannot in any decisive way have influenced the result regarding the duration of tuberculin allergy in my material (under point C).

CHAPTER VIII

BCG-Vaccination of Infants in Stockholm's Maternity Hospitals or during Their First Six Months of Life. Stockholm 1945—52

A. Introduction

With increasing experience more and more workers in this field recommend BCG-vaccination of newborn infants. The main reasons for this are the bad prognosis for tuberculosis in infants (Price 1949, Wallgren 1952 among others), and that the whole procedure is very much easier at this age (e.g. pre-vaccination tuberculin tests can be omitted). Wilson (1947) indicates that there is a very limited antibody-production activity during infancy, and he does not believe in BCG-vaccination at this age. However, investigations performed and experiences gained during recent years (Vahlqvist 1949, Peterson & Christie 1951, Osborn, Dancis & Julia 1952) indicate that the newborn infant has a considerable capacity for antibody-formation even if not comparable with that of the adult. The experience gained in Sweden from BCG-vaccination of infants since 1943 actually supports this view (Malmros 1949). Other arguments against vaccinating infants, such as lower rate of tuberculin inversion, increased incidence of complications and post-vaccinal gastro-intestinal disturbances have proved fallacious (Hertz 1949 among others); although a certain retardation of the increase in weight may sometimes be seen (Gyllenswärd 1949). It should be noted that the tuberculin inversion is, as a rule, somewhat delayed in the newborn and infants. The inversion rate at the time of post-vaccinal testing is, however, reported to be more than 90 per cent (Hertz 1949, Malmros 1949, Purser 1954).

B. BCG-Vaccination in Stockholm's Maternity Hospitals

BCG-vaccination in Maternity wards as a routine procedure was introduced in Sweden by Malmros and Wallgren in 1943. It is voluntary.

TABLE 39

BCG-vaccination in newborn infants in Maternity hospitals in Stockholm 1945—52.

Year	In Maternity hospitals					
	Total BCG-vaccinated		On mother's request, without known tb. environment	Total BCG-vacc.	Born alive	Percentage vaccinated
	Mother	Environment				
1945	76	—	1,114	1,220	14,866	8.2
1946	638	678	1,534	2,850	11,144	20.1
1947	681	624	3,593	4,898	13,650	36.0
1948	691	824	6,292	7,807	13,334	58.5
1949	700	700	8,683	10,083	13,395	75.3
1950	772	880	9,319	10,971	14,020	78.3
1951	663	1,017	9,899	11,549	13,132	87.9
1952	656	1,440	10,633	12,729	13,663	93.2
Total	4,877	6,163	51,067	62,107	110,204	—

Mainly those infants born in Maternity hospitals or similar institutions are vaccinated at birth. Deliveries at home, however, become more and more uncommon in Sweden. Thus, in 1930 7.3 per cent of all births in Stockholm occurred at home, the rest in hospitals. In 1940 the corresponding figure was 2.5 per cent; in 1945 2.4 per cent and in 1948—49: 0.7 per cent.

At the Maternity hospitals the selection of infants to be BCG-vaccinated as well as the vaccination technique is generally made by the pediatrician. If the child is ill, injured or premature vaccination is postponed. As a rule, 0.2 ml (0.1 mg) is given intradermally in the left thigh.

The number of BCG-vaccinations performed in Maternity hospitals in Stockholm is given in Tab. 39. It should be noted that between 1,000 and 2,500 mothers not residing in Stockholm are annually delivered in Stockholm's Maternity hospitals. As will be seen, the start in 1945 was on a modest scale, with only 8.2 per cent vaccinated, whereas in 1952, 93.2 per cent of all such newborn infants were vaccinated.

C. Children BCG-Vaccinated during Their First Six Months

When this investigation was made in Spring 1951, no children who had been vaccinated in the Maternity hospitals had reached actual school age.

TABLE 40

Percentage division into social classes among children BCG-vaccinated at birth or during their first six months in comparison with the main material.

	Number	Social Classes		
		I %	II %	III %
BCG-vaccinated during first six months (1939-45)	113	18.6	40.7	40.7
The main material	3,955	9.6	26.0	64.4

The material includes 39 children who had been BCG-vaccinated during their first six months. In 43.4 per cent of these cases there was a family history of tuberculosis, and in most cases this was probably the reason why prophylactic measures had been taken. The corresponding figure for the total number of vaccinated children in this material is 11.9 per cent.

These 39 children have been followed for *not less* than 7 years, and show 13.3 per cent reversion of tuberculin reaction. This group is too small to permit a conclusive comparison with other groups, all the more so as the period of observation after vaccination varies greatly (from 9 to 14 years). The number of reverters in the corresponding group of the whole material is 3.5 per cent after 7 years.

D. Children BCG-Vaccinated at Birth or during Their First Six Months

The small above-mentioned group does not provide sufficient material for a comparison between children vaccinated during early infancy and those vaccinated during their first year at school (see Ch. VI).

I therefore decided to make a separate study of children beginning school in Autumn 1951. Two schools were selected—Adolf Fredrik and Kungsholm. 74 of the children in beginner's forms had been vaccinated at birth in 1945 (i.e. belonged to material presented in Tab. 39) and had shown a positive post-vaccination tuberculin reaction at control in Infant Welfare Centres.

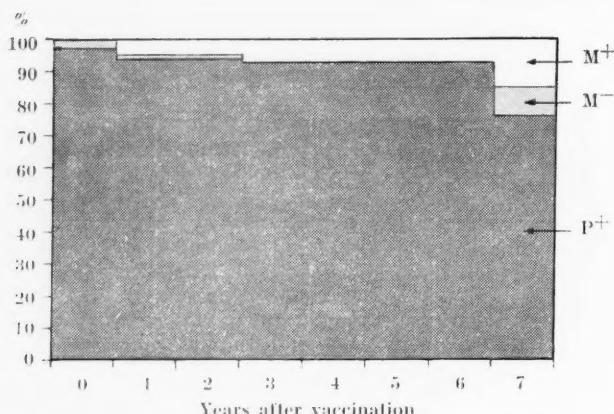


Fig. XXVII. Decline of allergy in 113 children, successfully BCG-vaccinated at birth or during the first six months of life (39 children from the large material and 74 from a separate additional material).

This makes a group of 113 (39 + 74) children—all BCG-vaccinated during their first six months of life. When this group is divided according to social class an apparent shift to the upper class is found as compared with the main material,—see Tab. 40.

A likely explanation here is probably to be found in a better understanding of the then "new" method.

The tuberculin tests of this last group, 74 children, have been sporadically and incompletely checked at the Infant Welfare Centres. Thus the course of tuberculin allergy during the first 7 years of life can, on the whole, only be judged from the initial and final tuberculin tests. The 39 children belonging to the main material, on the other hand, have been frequently checked, and reliable data are available. The children have been registered according to the previous year's tuberculin test until a new tuberculin test has been performed (as in Ch. VII page 88).

With this procedure it is found that tuberculin allergy in children who have been vaccinated at birth or during their first 6 months follows the course shown in Fig. XXVII. The number of reverters after 7 years is here 15 per cent—considerably more than in children vaccinated on beginning school, yet satisfactory. It is also seen that the positive Patch test reaction is rather well retained.

CHAPTER IX

General Summary

With this follow-up I have aimed at trying to answer questions about the value of BCG-vaccination in children of school age in a country where tuberculous infection and disease is relatively infrequent.

In the *Introduction* I begin by emphasizing the difficulties—ever present, and perhaps especially so in Scandinavia—in getting an adequate control for a large BCG-investigation that is statistically free from criticism. Even with dissimilar control materials—my and similar series can be of value. Social factors have not been given sufficient attention in previous surveys. The author gives an account of his motives for this investigation, its planning and a general account of the Swedish school system.

Chapter I begins with a short historical survey of the lead-up to BCG-vaccination, as well as the principles behind its use. Excellent work has been published in this connection, to which the reader is referred. How BCG-vaccination came to be introduced in the 1920's in Sweden—using the then "new" intradermal technique of Wallgren—is briefly described together with an account of how Scandinavia has become a leader in this type of prophylaxis.

Afterwards the conceptions and meaning of immunity to and resistance against tuberculosis, as well as the relation between immunity and tuberculin allergy, are discussed. These questions have been hotly debated in earlier literature, and the author tries to emphasize the most important of the present basic definitions and conclusions. The author stresses that tuberculin sensitivity and immunity to tuberculosis are two different things, but that from a practical viewpoint one can regard tuberculin sensitivity as an indication of immunity. Many exceptions exist, but not so many, however, as to disprove the rule. There are no other practical ways of judging immunity against tuberculosis at present and the estimation of antibodies has not yet shown itself to be utilisable here.

The author then goes deeper into previous work about the duration of

tuberculin allergy following BCG-vaccination and points out the usually divergent and poorly-systematised results obtained from different methods, materials and investigators. The duration of tuberculin allergy following BCG-vaccination can be said to be an approximate yardstick of the duration of relative protection.

The standard requirements which have been created for investigations of the use of BCG in the prevention of tuberculosis are discussed. The author touches on the difficulties in fulfilling some of these requirements in countries where tuberculosis is less frequent; especially the alternate selection of controls and the comparison of the mortality rate. In addition, a tabular survey of the literature, giving the more important BCG-vaccinated materials (above all intracutaneous) which quote resistance produced by this, is shown. On account of the variability of their presentation, these results have, to a certain extent, had to be shown schematically. Those series which have had a relatively satisfactory control material have been included in this survey. The protection has been expressed as a "protection percentage" of those vaccinated. Finally, the author has given a short account of the conception—superinfection, and of what part this plays in the duration both of tuberculin allergy and immunity against tuberculosis.

Chapter II deals with the socio-medical status of Stockholm and its Elementary schools, which are the foundation of this material: Thus, population statistics concerning the total number of children born in Stockholm and of the pupils in its Elementary schools, are given. Furthermore, a brief survey of the Health Care, the organisation of tuberculosis prophylaxis within the city's school administration, is given. Voluntary BCG-vaccination has been given a detailed description—as to how it started in 1942 and has now come to embrace some 40,000 school children. This vaccination is usually performed in the beginners' forms, according to Wallgren's technique: 0.05–0.1 mg BCG-bacilli intradermally. Afterwards the tuberculosis morbidity and mortality among school children in Sweden and in Stockholm's Elementary schools is given, and how this has decreased during the latter years to a very small total. The annual infection risk for tuberculosis during school years—estimated from different series—can be worked out at between 1 per cent and 4 per cent.

Chapter III puts forth questions, the answering of which is the main task of this thesis, and the author's aim in the following chapters. The fact that the natural resistance against tuberculosis is highest in the early

school years does not influence the judgment of the effect of BCG-vaccination, and of the duration of allergy during these years; neither is it a hindrance for prophylactic procedures—with the increasing morbidity during puberty and on the commencement of work kept in mind.

Chapter IV describes the choice of material, which schools and age groups are involved—taking into consideration the later-discussed social factors. The tuberculin test technique used (Patch test and Mantoux 100 TU) is also described, which is the same as that usually used in Stockholm's Elementary schools; in addition, the way of collecting information is given.

My material comprises 4,005 tuberculin tested children of the ages 9 to 16 years, and coming from seven schools (Spring 1951). 100 (2.4 %) "registered" children were not tuberculin tested for reasons given; but, however, there was no tuberculous disease among them. In addition, 50 children must be excluded from the statistical calculations as complete history details were not available, but none of these had clinical tuberculosis, either.

After this the author describes the actual general tuberculin allergy situation (Spring 1951): the percentage of positive Patch tests is seen to diminish slightly with increasing age. The Patch test seems to be reliable as an initial routine test, it being equivalent to Mantoux 10 TU, in any case up to the age of 12, and no noticeable sex difference could be seen in this respect.

78.7 per cent of the 3,955 school children were successfully BCG-vaccinated earlier during the period 1939—50, and only 2.8 per cent of these were tuberculin negative at the follow-up control (Spring 1951). In spite of the differently localised schools from which all these children came from, the vaccination frequency was tolerably similar between them. The total number of spontaneously positive children in the forms increased from 5.9 per cent in the 9 and 10 year olds up to 14.4 per cent in the 11 to 16 year olds, an increase of 8.5 per cent in those 5 to 6 years. Because these figures concern different age groups and the percentage BCG-vaccinated also varies, the annual infection risk cannot be worked out from these figures.

78.9 per cent of the 3,112 BCG-vaccinated children were inoculated through the schools' organisation, and of these, 2,046 (63.7 %) in the beginners' forms. Diagrams of the children's ages at vaccination and the time of this are shown, illustrating how the observation groups have been created and how the observation time following vaccination varies.

The risk of getting tuberculosis through previous or current occurrence of tuberculosis in the family or environment within this material has been charted. The occurrence of a tuberculous environment is the same (8.2 %) among the tuberculin negative - previously successfully BCG-vaccinated, and among the tuberculin negative - unvaccinated school children. Among the vaccinated - still tuberculin positive children the frequency of a tuberculous environment is slightly higher (12.0 %) which difference is, however, not statistically significant when compared with the former figure for the negative - vaccinated children. The spontaneously tuberculin positive children showed a frequency of tuberculous environment of 28.7 per cent. This difference is of the highest statistical significance when compared with the tuberculin negative - unvaccinated children. When comparing the total vaccinated with the total non-vaccinated children, the frequency of a tuberculous environment is statistically significantly higher among the latter. Of those children who were tuberculin negative at the beginning of school, 10 per cent of the non-vaccinated and 6.7 per cent of those vaccinated had a tuberculous environment. This difference is statistically significant.

Chapter V concerns the judgment of some social factors in the material. The socio-economic status of a group is of major importance in approaching tuberculosis problems. BCG-vaccination is one of many methods used in the fight against tuberculosis, and the author has examined this in relation to the social classes and overcrowding.

The judgment of and division into social classes in this material is then described. This has a lower social classification than the population of Stockholm in general, which fact the author tries to explain. It is further shown that in the case of 201 of the 515 tuberculin negative - unvaccinated children, the parents refused vaccination, and these were fairly evenly distributed within the different social classes, as in the main material. Vaccination refusers are found in all social classes in equal proportions.

When considering the division of the school children into social classes, one finds that the percentage of vaccinated children is equal in all social classes irrespective of the district involved. *School BCG-vaccination embraces all social classes in Stockholm to an equal degree.*

There is a moderate tendency for a larger percentage of spontaneously positive children to occur in the lower social classes than the higher, but this is not even statistically significant in the district containing mainly factory workers. *Thus one can no longer (in Stockholm) call*

tuberculosis a "disease of the poor" i. e. especially bound to the social class III.

A survey of the housing standard of the children has been made. Criteria for the judgement of this are given. The families of one half of the pupils were found to have a satisfactory living space, while 1/5th were "overcrowded". Crowding varied much between different districts. In comparison with the official statistical information regarding Stockholm's population, the children of this material had, on the whole, an inferior housing standard. *The author cannot demonstrate any statistical difference whatever between the division—according to housing space—for the vaccinated and non-vaccinated children. Overcrowding is no greater among the spontaneously positive children, with or without earlier clinical signs of tuberculosis, than in any other group.*

Chapter VI describes the occurrence of tuberculosis among the vaccinated and non-vaccinated children.

Of the 843 non-vaccinated children, there were 328 spontaneous inverters. 46 per cent of these had shown signs of clinical tuberculosis. The occurrence of clinical tuberculosis among the spontaneously positive children was significantly more frequent in school group S, where the social conditions were worse than in the other school group. The different types of clinical tuberculosis contracted were accounted for, of which 91.3 per cent were of a primary nature. Those children who had shown signs of clinical tuberculosis had a significantly more pronounced tuberculin sensitivity than those who became spontaneous revertors without clinical symptoms.

The ages at which spontaneous infection occurred are given, and it is seen that 128 of the 328 children contracted their infection after the beginning of school. 42 of them had shown signs of clinical tuberculosis.

Of the 3,112 children who had previously been successfully BCG-vaccinated, 7 had suspected or verified human superinfection with clinical symptoms. A detailed history of these 7 cases is given. Two of them occurred prior to school, and a further 2 had been vaccinated before school age. All of these 7 cases came from tuberculous families. In 4 of these cases the interval between the last positive tuberculin test and the infection was 9 months or less. None of these 7 children were thought to be revertors prior to the actual superinfection.

In all these 7 cases the tuberculosis infection was of a mild nature; in 4 it was clearly primary tuberculosis. In 4 cases culture of the stomach irrigation fluid was carried out—without finding any tubercle bacilli, however.

For a comparison between the vaccinated and unvaccinated groups a *survey table* is given on page 79. This shows the material's composition at different times: —before school, at the beginning of school, during school years and at the end of the investigation.

No comparison between the mortality of vaccinated and non-vaccinated children could be made, because during the investigation time (school time) no cases of death from tuberculosis occurred in any group.

This investigation seems to fulfil the standard requirements according to Park, with the exception of the control material; the cause of this has been previously explained.

Regarding the author's control material, it is furthermore pointed out that there is a fully comparable status with the vaccinated children concerning division into social classes, amount of living space in homes, race, sex, age and living districts. Unvaccinated children show a somewhat higher occurrence of tuberculous environment, but this can possibly be explained by such factors as the more thorough scrutiny of cases of clinical tuberculosis. Therefore, in this connection the initial state of both groups must be considered similar.

In a comparison between vaccinated and non-vaccinated children the author comes to the relations shown in Tab. 41.

At the first of the there mentioned comparisons between the tuberculosis morbidity in BCG-vaccinated and non-vaccinated children, one gets the relationship 1:79. The protection of those vaccinated is 99 per cent. On excluding those from both groups who had clinical tuberculosis before school age, one gets the relationship 1:39. In this case protection of those vaccinated is 97 per cent. With consideration to the observed person-years at the latter comparison, one gets the relationship 1:35, i.e. an equally great protection of those vaccinated, 97 per cent.

If one, on the other hand, compares those who were tuberculin negative at the beginning of school, the relationships between tuberculosis morbidity in BCG-vaccinated and non-vaccinated will be 1:54, and when regard is taken of the observed person-years, 1:48, i.e. the protection of those vaccinated will be 98 per cent in both instances. In spite of the high natural resistance children of this age have, the protective effect of BCG-vaccination has shown itself to be very obvious.

Chapter VII deals with the duration of tuberculin allergy following successful BCG-vaccination as well as other problems in connection with this. In the beginning, an account of different techniques for tuberculin testing and types of tuberculin, is given. At the tuberculin follow-up

TABLE 41
Clinical tuberculosis at follow-up examination.

	Number of children	Person/yrs. of observation. Total	% known tub. environment.	‰ clinical tb. cases	Clin. tb. cases per 1,000 person/obs. yrs.
Total vaccinated	3,112	—	11.9	2.25	—
Total non-vaccinated	843	—	16.1	177.9	—
When cases of clinical tuberculosis before school age are excluded:					
Vaccinated	3,110	11,519 ^a	11.8	1.61	0.43
Non-vaccinated	740	3,299 ^b	12.9	63.5	14.3
When only children, tuberculin negative and unvaccinated on starting school, are considered.					
Vaccinated	2,458	9,804 ^c	6.7	1.22	0.31
Non-vaccinated	643	2,830 ^b	10.0	65.3	14.8

a - from the beginning of school, and if then unvaccinated, from the time of vaccination.

b - from the beginning of school.

c - from the time of vaccination.

control of BCG-vaccinated individuals one ought to use tuberculin made from the same strains as the BCG-vaccination is aimed to protect against (according to quoted authors). Inversion following BCG-vaccination, initial post-vaccination (6 weeks) control tests as well as local vaccination reactions are not dealt with in this thesis.

One ought to aim at as long a tuberculin allergy as possible following BCG-vaccination. *In this material an average of 1 per cent annually of those successfully BCG-vaccinated became negative. This reversion risk is fairly constant from the first to the ninth school year, i.e. as long as I was able to follow the material. Thus, at the end of the ninth year, 91.6 per cent of the children were still tuberculin positive.*

The material has been divided up into groups which were vaccinated at the same time and at the same ages. The decline of tuberculin sensitivity of all these groups during the passage of years was gradual and very slight, varying from between 0.5 and 1.5 per cent annually. Here, there

is a certain connection with the frequency of a tuberculous environment, so that the decline of allergy in a group is less if the environment frequency is greater. The possibilities for superinfection, in the main, and its significance for the duration of the tuberculin allergy, is accounted for.

The diminution in the intensity of the tuberculin reaction from a positive Patch test to positive Mantoux 100 TU is greater throughout, and varies more—between 2.5 and 13.7 per cent annually.

Re-vaccinated children have been separately accounted for. These comprise only 1.57 per cent of the total vaccinated. The duration of tuberculin allergy after the first vaccination among these children was short, namely an average of 1.9 years.

In *Chapter VIII* an account is given of the increasing BCG-vaccination of newborn babies in Maternity wards. This has distinct advantages, and the customarily quoted disadvantages seem to be of less import than is usually thought. Nowadays, about 90 per cent of newborn babies in Sweden are BCG-vaccinated at the mother's request and according to this system. In the author's main material there were only 39 babies who were vaccinated at birth or during their first six months. There is a separate material—74 children, born during 1945 and vaccinated in the Maternity wards, whom the author has separately investigated in the Autumn of 1951 when they came to form I. This additional material of altogether 113 children, *BCG-vaccinated shortly after birth, showed just over 2 per cent reverters per year*, so that after 7 years some 15 per cent had become tuberculin negative.

It can thus be stated that the duration of tuberculin allergy in children intracutaneously BCG-vaccinated while in the first forms at school is very good, and good when babies are vaccinated shortly after birth or during their first six months. As one is trying to get as long a period of tuberculin positivity as possible, these results are extremely satisfactory.

With the guidance of this experience, the author will outline a BCG-vaccination program (for the ages 0—21) as follows:—

Shortly after birth:	BCG-vaccination (without pre-vaccination tuberculin test).
On starting school: (7 years of age)	Tuberculin test, vaccination of unvaccinated, and re-vaccination of possible reverters.
Ending school: (14—15 years of age)	Tuberculin test, vaccination of unvaccinated, and re-vaccination of possible reverters.

At 20 years of age:
(Conscripts, etc.) Tuberculin test, vaccination of unvaccinated, and
re-vaccination of possible reverters.

This would be generally every seventh year of life, and by means of such a vaccination program the increased risks of tuberculous diseases in infancy and puberty as well as adolescence should be, to a large degree, reduced.

Zusammenfassung

Diese Untersuchung beabsichtigt Fragen zu beantworten, die den Wert der BCG-Vaccination bei Schulkindern betreffen in einem Land, wo tuberkulöse Infektion und Erkrankung relativ selten sind.

In den einleitenden Kapiteln werden die Fragestellungen erörtert, ein kurzer historischer Abriss über die BCG-Vaccination gegeben und ein Überblick sowohl über die massgeblichen Ansichten auf diesem Gebiet als auch über die Tuberkulose und den Tuberkuloseschutz in den Stockholmer Volksschulen.

Das Material besteht aus 3 955 bis zum Jahre 1951 genau kontrollierten und tuberkulinuntersuchten Kindern aus sieben Schulen in Stockholm, wovon 2 046 Kinder in den Schulanfangsklassen 1945—1949 BCG-vacciniert wurden. Insgesamt waren 3 112 Kinder (78,7 %) vor oder in der Schule BCG-vacciniert. Die übrigen Kinder waren Kontrollmaterial, das nicht nach besonderen Gesichtspunkten ausgewählt wurde, da ein solches Verfahren in Skandinavien bei BCG-Vaccinationen nicht durchführbar ist.

Das Vorkommen von tuberkulöser Umgebung bei Kindern ist nachgewiesen und, wie erwartet, bedeutend häufiger (28,7 %) bei spontanpositiven Kindern als bei den BCG-Vaccinierten, noch immer tuberkulinpositiven (12,0 %) und den übrigen Gruppen (8,2 %). Die Verteilung von sozialen Faktoren sind in Beziehung zu den medizinischen gestellt worden. Dabei zeigte sich, dass die BCG-Vaccination gleichermaßen alle sozialen Gruppen in Stockholm umfasste. Statistisch findet man auch keinen Unterschied in der Verteilung der klinischen Tuberkulose in den verschiedenen Sozialgruppen. Die Art der Wohnungsverhältnisse ist gleichmäßig verteilt in sowohl der BCG-vaccinierten als auch der nicht-vaccinierten Gruppe von Kindern und die besonders engen Wohnungsverhältnisse sind nicht häufiger bei den spontanpositiven Kindern.

Während der Observationszeit, also in diesem Falle die Schulzeit, ist kein Todesfall an Tuberkulose zu verzeichnen gewesen, weder bei den BCG-vaccinierten noch bei den nichtvaccinierten Kindern. Die Observationszeit schwankt zwischen 2½—9 Jahren. Bei den Kindern, die bei Schulbeginn tuberkulinnegativ und nicht BCG-vacciniert waren, findet man im späteren Verlauf klinische Tuberkulose bei sowohl später BCG-

vaccinierten als auch nichtvaccinierten Kindern in einem Verhältnis 1:54 oder im Hinblick auf die observierten Personen/Jahre 1:48. Der Schutz ist in beiden Fällen 98 % für die Vaccinierten. Die sieben Kinder, die BCG-vacciniert waren und sich später eine klinische Tuberkulose zuzogen werden besonders erörtert. Weitere Fragestellungen werden discutiert.

Tuberkulinallergi und Tuberkuloseimmunität sind zwei verschiedene Sachen, aber aus praktischem Gesichtspunkte ist die Tuberkulinreaktion ein in den meisten Fällen brauchbarer Indikator für die Feststellung von erworbener Immunität gegen Tuberkulose. Man sollte eine möglichst lange postvaccinale Tuberkulinallergi nach der BCG-Vaccination erstreben. In diesem Material schlägt im Durchschnitt nur 1 % der erfolgreich Vaccinierten jährlich um zu einer negativen Tuberkulinreaktion. Am Ende des neunten Schuljahres sind immer noch 91.6 % der Kinder tuberkulinpositiv, die am Schulbeginn BCG-vacciniert wurden mit positivem Ausschlag. Verschiedene Altersgruppen, die zu verschiedenen Zeitpunkten vacciniert wurden, zeigen im grossen Ganzen das gleiche aus Vaccinationsgesichtspunkt zufriedenstellende Resultat.

In einem Spezialmaterial von Kindern, die bei der Geburt oder während des ersten Lebenshalbjahres BCG-vacciniert wurden, findet man nach sieben Jahren immer noch 85 % tuberkulinpositive Kinder.

Unter Verwendung von obengenannten Erfahrungen skizziert der Verfasser ein BCG-Vaccinationsprogramm für die Altersklassen bis zu 21 Jahren.

Résumé

Ce travail complémentaire a pour but de répondre aux questions concernant la valeur de la vaccination du BCG sur les enfants en âge scolaire dans un pays où l'infection et la maladie tuberculeuses sont relativement peu fréquentes.

Les premiers chapitres indiquent les diverses façons dont le problème se pose et donnent un bref historique de la vaccination du BCG, tout en rendant compte des théories élaborées pour chacune des questions signalées. L'auteur indique, de plus, ce qui en est de la tuberculose et des mesures prophylactiques contre la tuberculose dans les écoles primaires de Stockholm.

L'examen a été mené sur 3 955 enfants provenant de 7 écoles de Stockholm: ils ont été soigneusement contrôlés et soumis à l'épreuve de la tuberculisation jusqu'à 1951. 2 046 d'entre eux avaient reçu le BCG à leur entrée à l'école entre 1945 et 1949. En tout, 3 112 enfants avaient été vaccinés par le BCG (soit 78,7 %) avant ou dans l'école. Les autres enfants ont servi d'éléments de contrôle. On ne les a choisis ni au hasard, ni selon des critères très rigoureux, car une telle manière de faire n'est pas possible en Scandinavie lorsqu'il s'agit de la vaccination du BCG.

L'auteur rend compte de l'existence du milieu tuberculeux sur les enfants: celle-ci est, comme on s'y attendait, sensiblement plus grande (28,7 %) sur les enfants à réaction positive naturelle que sur les enfants vaccinés par le BCG — et qui ont encore une réaction tuberculinaire positive — (12 %) et sur les autres groupes (8,2 %). Les conditions sociales et celles de logement sont constamment notées, et ces divers facteurs ont été mis en relation avec les facteurs médicaux. Il apparaît que la vaccination BCG est étendue de façon égale à tous les groupes sociaux de Stockholm. De même les statistiques n'indiquent pas de différences dues à des causes sociales en ce qui concerne la diffusion de la tuberculose clinique. Les dimensions du logement se retrouvent dans la même proportion tant chez les vaccinés que chez les non vaccinés, et l'on n'a pas noté que les enfants à réaction positive naturelle habitent plus souvent que les autres dans des logements peu spacieux.

Durant le temps consacré aux observations — dans le cas présent,

durant le temps de fréquentation de l'école —, on n'a enregistré aucun cas mortel ni dans le groupe des vaccinés par le BCG, ni dans celui des non vaccinés. Le temps durant lequel les enfants ont été en observation varie de $2\frac{1}{2}$ ans à 9 ans. Parmi les enfants à réaction tuberculinique négative au moment de leur entrée à l'école, on constate une tuberculose clinique chez les vaccinés et les non vaccinés dans le rapport de 1 vacciné sur 54 non vaccinés, ou bien, si l'on tient compte du nombre d'années des enfants observés, de 1 sur 48. Dans les deux cas, pour les vaccinés on constate 98 % d'épargnés. Les 7 enfants qui ont été atteints de tuberculose clinique et qui avaient auparavant été vaccinés par le BCG font l'objet d'une enquête approfondie. L'auteur expose ensuite d'autres problèmes connexes.

L'allergie à la tuberculine et l'immunité contre la tuberculose sont deux choses différentes, mais du point de vue pratique, la réaction tuberculinique suffit dans la plupart des cas à indiquer l'immunité acquise contre la tuberculose. Il faut s'efforcer de réaliser une allergie tuberculinique aussi prolongée que possible après l'injection du BCG. Chez les enfants examinés, il n'y a eu en moyenne par année que 1 % de vaccinés qui soient revenus à une réaction négative à la tuberculine. A la fin de la neuvième année scolaire, 91,6 % des enfants vaccinés la première année de l'école et à réaction positive, avaient encore une réaction tuberculinique positive. Un résultat pratiquement identique et très satisfaisant du point de vue vaccination a été enregistré dans les différents groupes d'âges, vaccinés à différentes époques.

Chez des enfants examinés à part et qui avaient reçu le BCG à leur naissance ou dans leurs premières, demiannées, on en trouve 85 % qui, après 7 ans, ont toujours une réaction tuberculinique positive.

S'appuyant sur les expériences susdites, l'auteur esquisse un programme de vaccination du BCG pour les différents âges jusqu'à la 21ème année.

Resumen

Este estudio persigue responder a ciertas preguntas respecto al valor de la vacunación con BCG, en lo que se refiere a niños en edad escolar, y en un país en que la infección y la morbilidad tuberculosa son relativamente poco frecuentes.

En la introducción se presenta el problema, junto con una breve reseña histórica acerca de la vacunación con BCG, y una descripción de los puntos de vista más relevantes al respecto. Se da además una información acerca de la tuberculosis y las medidas de protección antituberculosa en las escuelas de Estocolmo.

El material en que se basa este estudio, consiste en 3955 niños, de 7 escuelas de Estocolmo, todos ellos cuidadosamente controlados y con tuberculinoreacción. De entre ellos 2046 fueron vacunados con BCG durante su primer año escolar, entre los años 1945—49. La cifra total de los que recibieron vacunación asciende a 3112 (78,7 %). El resto de los niños ha servido como grupo de control, aún cuando no fué elegido al azar o alternativamente, ya que tal procedimiento, por lo menos en lo que se refiere a la vacunación con BCG, es impracticable en Escandinavia.

Analizando los antecedentes de contactos tuberculosos de los niños, se encuentra, como es de esperar, que ellos son significativamente más elevados (28,7 %) entre los niños espontáneamente tuberculinopositivos que en los niños persistentemente tuberculinopositivos después de la vacunación con BCG (12,0 %), y que en los otros grupos (8,2 %). Se estudia la repartición de los casos entre los diferentes grupos sociales y en relación a las variadas condiciones de vivienda, y la posible relación de estos factores sociales con los factores médicos. Se demuestra que la vacunación con BCG se extendió en igual forma entre los distintos grupos sociales. La diversidad en las condiciones de habitación estaba igualmente distribuida entre los grupos de niños vacunados como no vacunados. No pudo demostrarse, entre los niños espontáneamente tuberculinopositivos, una mayor densidad de personas por habitación que en los otros grupos.

Durante el período de observación — en este caso los años escolares — no se han observado defunciones, ya sea entre los niños vacunados con BCG como entre los no vacunados. El período de observación ha variado

entre 2 ½ a 9 años. Entre los niños que eran tuberculinonegativos al entrar a la escuela, los casos de TBC clínica se han distribuido en una proporción de 1: 54 entre los niños vacunados y los no vacunados. Si la comparación se hace en función de persona-año, la proporción resulta ser de 1:48. En ambos casos puede demostrarse una protección ascendente al 98 % para los niños vacunados con BCG. Se describen en detalle los casos de 7 niños vacunados con BCG que posteriormente hicieron una tuberculosis clínica, discutiéndose el problema que estos casos plantean.

La alergia a la tuberculina y la inmunidad tuberculosa son dos cosas diferentes, pero desde un punto de vista práctico la tuberculinoreacción constituye en la mayoría de los casos un índice útil de la existencia de inmunidad antituberculosa. Conviene esforzarse en obtener alergia a la tuberculina por un tiempo tan prolongado como sea posible después de la vacunación con BCG. En el material aquí descrito, como promedio sólo un 1 % de las vacunaciones exitosas regresa hacia una tuberculinoreacción negativa al cabo de un año. Al término del 9º año escolar, el 91,6 de los niños que fueron vacunados en su primer año escolar, y que a raíz de la vacunación se hicieron tuberculinopositivos, siguen siendo tuberculinopositivos. En otros grupos, vacunados en edades diferentes, la vacunación ha demostrado aproximadamente el mismo satisfactorio resultado.

En un grupo especial de niños, vacunados con BCG al nacer o durante los primeros 6 meses de edad, se encuentra reacción positiva a la tuberculina en un 85 % de los casos al cabo de 7 años.

Basado en las experiencias aquí expuestas, el autor esquematiza un programa de vacunación con BCG para las distintas edades, hasta los 21 años de edad.

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TABLE 2
Resistance produced by BCG-vaccination

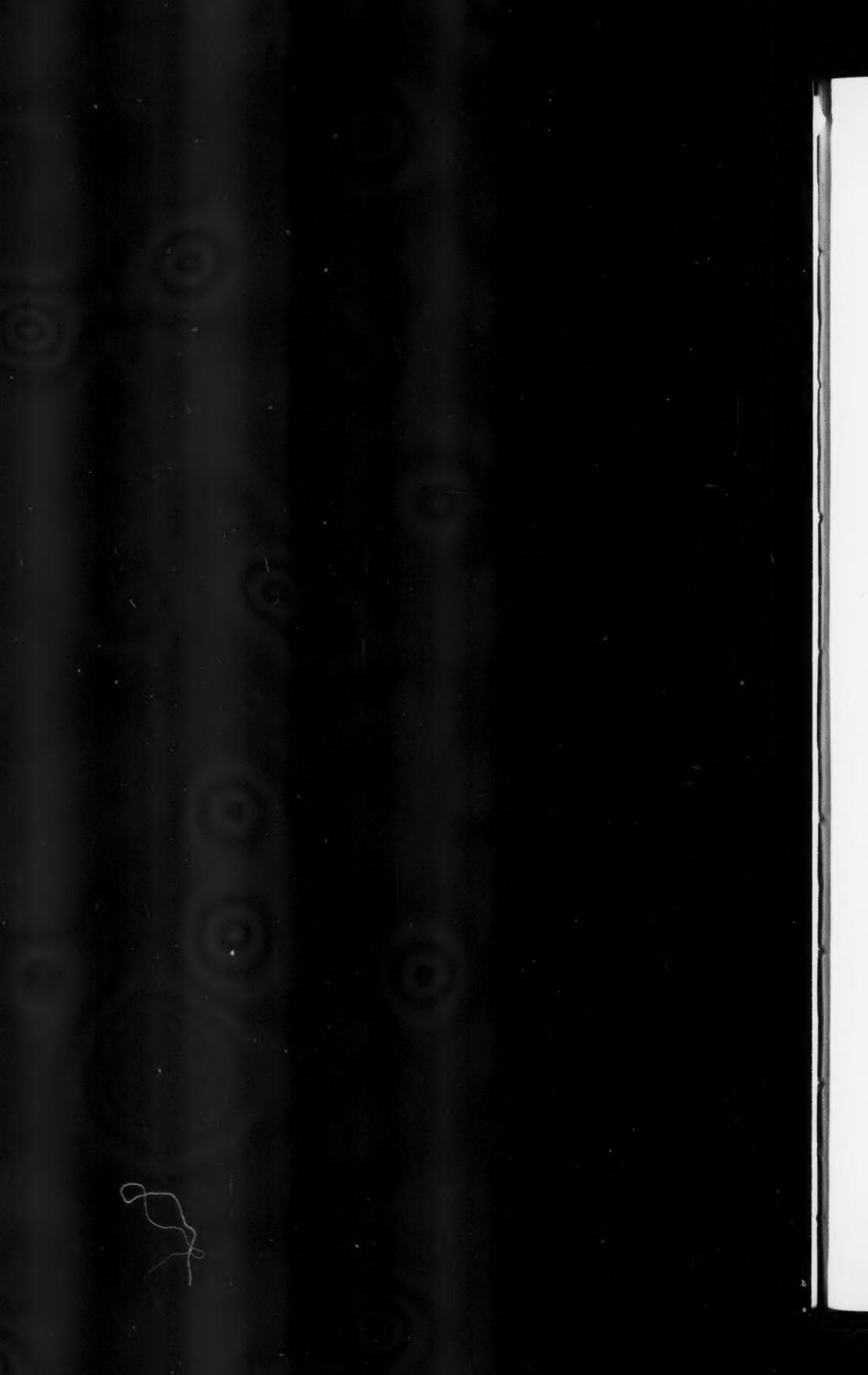
Author	Publ. year	Collect. year	Material	Vaccination- method & dose mg	Age at vacc. years	Number	Exposure %	Controls		BCG-vaccinated						Controls						Protection % of those vaccinated	
								Number	Exposure %	Years of obser.		Tuberculosis- morbidity		Tuberculosis- mortality		Years of obser.	Tuberculosis- morbidity	Tuberculosis- mortality		Morbid.	Mort.		
										Av. years	Total	% Total	per 1,000 person. obs. years	% Total	per 1,000 person. obs. years	Av. years	Total	% Total	per 1,000 person. obs. years				
<i>Oral</i>																							
Aldershoff & van den Berg	1932	26—32	Infants	Oral	Newborn + 97	128 100	70 53	100 100	1 2	5.5 4.1		2.3 2.1				1 2	17.8 24.5		10.0 18.9		69 83	77 89	
Aronson & Dan- nenberg	1935	27—34	Infants	Oral	Newborn + 14	41 15	100 uncertain	84 45	100 uncertain			2.4 0 0						11.9 4.4 0			— — 100		
Park & Keresztri	1936	26—35	Infants	Oral	Newborn	269	mixed	345	mixed			1.1						2.6			— 58		
Naeslund	1938	27—37	Infants	Oral	Newborn	13,300	mixed	31,000	mixed			0.15						0.63			— 92		
Hopkins (Baudouins mater.)	1941	26—38	Infants	Oral	Newborn	793	100	1,200	100		3.3	2.1				14.6 12.0	6.7 5.4		77 74	69 65			
<i>Multiple puncture</i>																							
Rosenthal, Leslie & Loewinsohn	1948	38—47	Infants	Rosenthal	Infants Newborn	1,417 151	unknown 100	1,414 105	unknown 100		5,627 517	1.95 3.86	0.17 0			6,032 284	6.46 17.60	1.16 14.09		70 78	85 100		
<i>Intracutaneous</i>																							
Heimbeck	(1936) 1948	26—48	Student nurses	Intrac. 0.05—0.10 (some subc.)	20	501	100	284	100	12—20	4,958	9.9		1.0	12—20	2,563	41.4		4.7	76	79		
Park & Keresztri	1936	26—35	Infants	Sub-or intrac.	1—12 m.	421	mixed	410	mixed	max. 8			0.07	max 8				0.27		74			
Scheel	1941	26—39	Medical students	Intrac. 0.02—0.10	20—25	334	100	272	100	3.5	1,182	12		3.0	825	43			72	—			
Dahl, Hertzberg & Refsum	1941	28—40	"Dispensär"- material	Intrac. 0.10—0.15		1,769			corresp.		1—12	3,955	0.76		1—6		1.76			57			
Kristensson	1942	29—39	Nurses	Intrac. 0.015—0.05	20—25	202	100	33	100	1—11		9.9			1—11	39.39			96				
Madsen, Holm & Jensen	1942		Students			249	64	863	40		317	0	0		1,950	6.0	27	0	100				
Winge	1942	35—42	Medical students	Intrac.		256	mixed	89	mixed			0.78	0			42.7		0		98			
Rinvik	1944	26—40	Children tbc. envir.	Intrac. 0.02—0.10		293	62	476	mixed	1—15		5.8	0			34.2		1.6	83	100			
Ferguson	1946	34—43	Nurses	Intrac. 0.20	20	1,005	mixed	759	mixed	2.42	0.895			2.54	3.82				77				
	34—43	Nurses		0.20	20	203	100	113	100	1.08	2.46			1.06	15.9				85				
	34—43	Medical personnel		Intrac. 0.20	20—25	470	100	274	100	1.19	1.92			1.44	11.7				84				
Levine & Sackett	1946	28—39	Children tbc. envir.	Intrac. 0.15	0—1	445 a) 556 b) 91 c)	50	545 528 96	50	5—16			0.68 1.41 1.1				3.38 1.51 3.1			80 7 65			
Törnell	1947	35—40	Children & adults	Intrac. 0.05—0.08		707	mixed	119	mixed	4	2,870	1.1	2.8		6.5	19.3	30.0		91				
Savilahti	1947	41—46	18—25 yrs soldiers	Intrac. 0.05	18—19	13,400	mixed	ea 13,000	mixed	6—8 m		3.0			0.37	2	5.7		1.57	47	76		
Hertzberg	1948	28—44	Average population	Intrac. 0.05—0.10	0—39	398 231 905	100 mixed unknown	741 302 1,350	100 mixed unknown	0—10 0—10 0—10	2.5 1.7 1.3			0 0.43 0	0—10 0—10 0—10	57.1 44.0 35.9		4.3 1.3 1.3		97 96 96	100 67 100		
	1940	26—48			0—94 0—95 0—96	849	mixed	2,826	mixed	5—600		1.6				21,669	9.8	0.6	82	100			

(Baudouins mater.)						mixed		mixed		3.1	1.9				12.0		5.4		74	65	
<i>Multiple puncture</i>																					
Rosenthal, Leslie & Loewinsohn	1948	38—47	Infants	Rosenthal	Infants Newborn	1,417 151	unknown 100	1,414 105	unknown 100	5,627 517	1.95 3.86	0.17 0		6,032 284	6.46 17.60	1.16 14.09		70 78	85 100		
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Heimbeck	1948																				
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Scheel	1941	26—39	Medical students	Intrac. 0.02—0.10	20—25	334	100	272	100	3.5	1,182	12	3.0	825	43		72				
Dahl, Hertzberg & Refsum	1941	28—40	"Dispensär"-material	Intrac. 0.10—0.15		1,769		corresp.		1—12	3,955	0.76	1—6		1.76			57			
Kristensson	1942	29—39	Nurses	Intrac. 0.015—0.05	20—25	202	100	33	100	1—11	9.9		1—11	39.39			96				
Madsen, Holm & Jensen	1942		Students			249	64	863	40		317 0	0		1,950	6.0	27	0	100			
Winge	1942	35—42	Medical students	Intrac.		256	mixed	89	mixed		0.78	0			42.7		0	98			
Rinvik	1944	26—40	Children tbc. envir.	Intrac. 0.02—0.10		293	62	476	mixed	1—15	5.8	0			34.2		1.6	83	100		
Ferguson	1946	34—43	Nurses	Intrac. 0.20	20	1,005	mixed	759	mixed	2.42	0.895		2.54		3.82			77			
Ferguson		34—43	Nurses	0.20	20	203	100	113	100	1.08	2.46		1.06		15.9			85			
Ferguson		34—43	Medical personnel	Intrac. 0.20	20—25	470	100	274	100	1.19	1.92		1.44		11.7			84			
Levine & Sackett	1946	28—39	Children tbc. envir.	Intrac. 0.15	0—1	445 a) 556 b) 91 c)	50	545 528 96	50	5—16		0.68 1.41 1.1					3.38 1.51 3.1		80 7 65		
Törnell	1947	35—40	Children & adults	Intrac. 0.05—0.08		707	mixed	119	mixed	4	2,870	1.1	2.8		6.5	19.3	30.0		91		
Savilahti	1947	41—46	18—25 yrs soldiers	Intrac. 0.05	18—19	13,400	mixed	c:a 13,000	mixed	6—8 m	3.0		0.37	2		5.7		1.57	47	76	
Hertzberg	1948	28—44	Average population	Intrac. 0.05—0.10	0—39	398 231 905	100 mixed unknown	741 302 1,350	100 mixed unknown	0—10 0—10 0—10	2.5 1.7 1.3	0 0.43 0	0—10 0—10 0—10	57.1 44.0 35.9		4.3 1.3 1.3		97 96 96	100 67 100		
Heimbeck	1949	26—48	Average population	Intrac. 0.01—0.05	0—20	842	mixed	2,836	mixed		5,409	1.6	0	21,662	8.8	0.6	82	100			
Hyge	1949	41—49	Schoolgirls	Intrac. 0.10	12—18	106	100	94	100	7.0	1.9	0	7.0		58.6		1.06	97	(100)		
Ferguson & Simes	1949	33—45	Infants N. Am. Indians	Intrac. 0.2—0.3 (21 oral)	Newborn	306	49.3	303	53.8	6.6	1.96	2.95	0.65	0.99	6.1	9.6	15.7	2.97	4.9	81	80
Dahlström & Difs	1951	41—46	20—25 yrs soldiers	Intrac. 0.05	20—22	36,235	mixed	25,239	mixed	3—5	0.46		0.50	3—5		1.24		1.51	63	66	
Aronson et al.	1952	35—51	0—20 yrs N. Am. Indians	Intrac. 0.10—0.15 0.10	0—20 Infants	1,551 123	c:a 50 139	1,457	c:a 50 139	13—15	21,241	11.7 3.3	0	0.56	13—15	19,520	29.0 8.0	3.32 2.9	60 59	83 100	
Nielsen	1953	36—46	Average population	Intrac. 0.10	0—35	3,248	mixed	10,438	mixed	5.8	18,573	0.48	0.05	5.7	70,728		1.27	0.21	62	76	
König & Schulze	1953	48—52	Infants & Children	Intrac. 0.05	0—15	591,871	mixed	2,389,573 also tub. pos.	mixed	1—3	0.03		0.017	1—3		0.34		0.14	91	99	
Daelen & Dix	1953	47—49	Children	Intrac. 0.05	3—18	70,424	mixed	92,145	mixed	4	0.06		4		0.35			83			

a) after selection method

b) after alternation method

c) with separation during incub. period



FROM THE PEDIATRIC CLINIC, UNIVERSITY OF LUND
(HEAD: PROFESSOR STURE SIWE, M.D.)

STUDIES ON SERUM LIPIDS
AND LIPOPROTEINS IN INFANCY
AND CHILDHOOD

BY

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CHAPTER I

INTRODUCTION AND PURPOSES OF THE PRESENT INVESTIGATION

Our knowledge about serum lipids and lipoproteins in normal infants and children is still incomplete. This applies above all to the first year of life. With the new micromethods now available for determining serum lipoproteins after electrophoretical separation on filter paper it has been possible to investigate the serum lipoproteins not only in umbilical cord blood, but also in newborns and infants. It was against this background that the present investigation was started.

Special interest was directed to the serum lipoproteins but in order to obtain a better understanding of the changes of serum lipids, also total lipids, total and free cholesterol and phospholipids were investigated simultaneously in the same serum. By means of micromethods all these analyses were performed with 0.6 ml serum. It was thus possible to carry out serial analyses even in newborn premature infants.

The purposes of the present investigation were:

- to study the changes in the serum lipids and lipoproteins during the first few days of life,
- to form an opinion of the time when serum lipids and lipoproteins reach values found in normal adults,
- to find out whether premature infants differ from fullterm infants with respect to the serum lipids and lipoproteins,
- to ascertain whether twins differ from one another with regard to the serum lipids and lipoproteins,
- to elucidate whether the diet may influence the changes in serum lipids and lipoproteins during the first few days of life.

CHAPTER II

EARLIER INVESTIGATIONS

SERUM LIPIDS IN INFANTS DURING THE NEONATAL PERIOD

In 1912 HERRMAN & NEUMANN found the level of the cholesterol esters and that of neutral fat to be lower in whole blood from the umbilical cord than in blood from normal women. As is seen in Table 1, in the course of the following years contradictory reports appeared concerning the serum lipids in umbilical cord blood (SLEMONS & CURTIS 1917, ROSENTHAL & MEIER 1921, PLASS & TOMKINS 1923 and SLEMONS & STANDER 1923). HELLMUTH (1926) studied the total lipids, the total cholesterol, total fatty acids and phospholipids in sera from 30 umbilical cords. He found the concentration of all lipid fractions to be significantly lower than for normal adults. The lipid values recorded in 4 infants delivered by Caesarian section were just as low as those found in the sera from the 30 children delivered by the normal route. BOYD (1936), who used oxalated serum, found the total lipids, the total and free cholesterol and phospholipids in umbilical cord blood to have lower values than those found by any of the other investigators. HORNUNG (1926) was the first to report increased total cholesterol during the first few days of life, and GYÖRGY (1926) reported that both the total cholesterol and phospholipids increase with age and that this increase was most pronounced during the first month of life. GORDON & COHN (1928), however, found no increase in the total cholesterol or phospholipids during the first few days of life.

The contradictory reports mentioned above are ascribable above all to the different methods used and to the fact that the extraction of serum lipids by these older methods was not complete. The determination of the different cholesterol fractions also offered difficulties until SCHOENHEIMER & SPERRY (1934) described their micro-

method. It may therefore be said that the results of serum cholesterol before 1934 can hardly be compared with those obtained by modern analytical methods.

In 1936, SPERRY, who used the method of SCHOENHEIMER & SPERRY, studied the total and free cholesterol in heparinized blood plasma from 63 children aged 4—25 days and in 7 specimens of umbilical cord blood. Unfortunately, not all of the samples could be analysed completely. "An unknown number of the first 24 samples analysed stood at room temperature for extended periods. While this investigation was in progress it was found, that a marked esterification with increase in the ratio of combined to free cholesterol, occurs under these conditions. It was necessary, therefore, to omit all of these results which included all of those on cord plasma, from the chart." He found a pronounced increase (76 per cent) in the total serum cholesterol during the first 3 to 4 days of life. In infants, aged 4—25 days, the total cholesterol values varied without any distinct tendency to increase or decrease. The ratio of combined to free cholesterol varied within a wide range, and in most cases it was lower than the minimum ratio found in adults.

SENN & McNAMARA (1937) studied the total lipids, total cholesterol, free cholesterol and phospholipids in serum from children 1—13 hours after birth and after a further 6—10 days. They used the micromethods of KIRK, PAGE & VAN SLYKE (1934). They found that "the amounts of both the total lipids and their fractions rose significant with increasing age during the neonatal period". It is of interest to note that in the serum of umbilical cord blood from 3 of 25 children SENN & McNAMARA did not find any phospholipids and that the mean value of phospholipids was much lower than those found by any of the other investigators. The mean levels attained by the infants 6—10 days old remained appreciably lower than those reported for adults, when measurements were made by the same chemical procedures. In 2 of the cases the total lipids were also determined at 6 weeks of age and found to have increased. The authors summed up their article with the words: "The disparity of values for plasma lipids between the neonatal period and adult life has not previously been sufficiently emphasized. Further studies are under way to determine the normal ranges and means at other

period in infancy and to ascertain the period during childhood when the measurements approach those of the adult levels. It is obvious that such standards must be established before significance is ascribed to deviations obtained from measurements on the plasma of sick infants and children." However, the authors have not published any investigation of these important problems. No investigations of serum lipids in the neonatal period had appeared from 1937 to 1954, when RAFSTEDT & SWAHLN (1954) published an article on total lipids, total and free cholesterol and phospholipids in serum from umbilical cord blood and in serum from the same infants 1—6 days after birth. The lipoprotein distribution in these specimens was also studied and is accounted for later in this chapter. During the first few days of life the total lipids, the total cholesterol and phospholipids showed a marked increase of about the same order as was found by SENN & McNAMARA.

SERUM LIPIDS IN INFANTS AFTER THE NEONATAL PERIOD

It is seen from Table 1 that in most of the earlier investigations carried out on children below 12 months the analytical methods used were less modern. As a rule it was the total cholesterol that was determined. (GYÖRGY 1926, MANICATIDE et al. 1927, BAYLAC & SENDRAIL 1928, GORDON & COHN 1928.) All the investigators noted values lower than those found in older children and adults. While MANICATIDE et al. could not demonstrate any increase during the first year of life, GYÖRGY found a marked increase during the first month of life followed by a slight increase during the rest of the first year. The investigators of phospholipids (GYÖRGY 1926, GORDON & COHN 1928 and KUGELMASS & GREENWALD 1931) also found lower values than for normal adults. GYÖRGY found that like the total cholesterol, the phospholipids increased slightly during the first year of life. HANSEN (1937) and RADWIN et al. (1940) used modern methods, but their materials consisted of only a few children and were therefore not representative. HODGE, SPERRY & ANDERSEN (1943), who used the same method as in the present investigation for determining total and free cholesterol, statistically ana-

lysed the determinations made in hospitalised children during the years 1934—1942. Not only children with diabetes, nephrosis, hypothyroidism or obesity were excluded, but also those who showed evidence of malnutrition, loss of weight, infection or anemia. Of the remaining patients, 417 were regarded as normal. They grouped their material according to age. The first age class (2—6 months) included 16 infants and the second age class (7—12 months) 27 infants. In both age classes they found the mean total cholesterol value to be the same as in normal adults or about 200 mg/100 ml. They stated that it may be concluded that by the second month of life the cholesterol concentration and the ratio of combined to free cholesterol have already increased from the low value at birth to the adult level, where they remain without further changes. However, for those infants who have lost body-weight they found a mean total cholesterol value of 121 mg/100 ml and for those infants, who were infected and had also lost weight, the mean total cholesterol value was 116 mg/100 ml. OFFENKRANTZ & KARSHAN (1936), who investigated children from 2 months to 12 years of age, found infection to have no demonstrable effect on the total cholesterol values in their large series. SPERRY (1936) had shown that in infants aged 4—25 days the amount of total cholesterol varies within wide limits with no apparent tendency to increase or decrease and that it has a mean value of 133 mg/100 ml. Neither SPERRY nor HODGE, SPERRY & ANDERSEN, however, demonstrated an increase in total cholesterol between the first and second month of life.

SERUM LIPIDS IN CHILDREN AGED 2—16 YEARS AND IN ADULTS

A survey of the most important investigations in children is given in Table 1, from which it is apparent that the most complete investigations were those carried out by THOMAS (1947), KORNERUP (1948) and WAMBERG (1954), who determined the total lipids, the total and free cholesterol and the phospholipids. It is clear that the results obtained in these three investigations are in good agreement. Neither KORNERUP nor WAMBERG could show any correlation between the serum lipid values and the age or sex of the child.

Neither did HODGE, SPERRY & ANDERSEN find any correlation between the age and the total cholesterol level. According to the investigators referred to above, no definite increase seems to occur with age after the first year of life, by when the serum lipids have reached values corresponding to those found in adults. On the other hand, GYÖRGY, GORDON & COHN, BAYLAC & SENDRAL as well as OF-FENKRANTZ & KARSHAN found lower cholesterol values for younger children than for older.

As to the increase in serum lipids in adults with increasing age, opinions differ. KORNERUP (1950) and others found the serum lipid content to vary only slightly with age and sex. KEYS et al. (1950) and BARR, RUSS & EDER (1952) and others found the total cholesterol level to increase after the age of forty.

SERUM LIPOPROTEINS IN INFANTS AND CHILDREN

In electrophoretic studies of serum from umbilical cord blood (Tiselius' macroelectrophoresis), LONGSWORTH et al. (1945) found that the α - and β -globulin components were smaller than in pregnant women or in normal adults. As the α - and β -globulins contained the major part of the serum lipids (BLIX, TISELIUS & SVENSSON 1941), they separated these two components together and determined the total lipid content in this globulin fraction. They found the lipid content of this fraction to occur in increasing quantity from umbilical cord blood, the normal adult and the pregnant woman, an increase parallel with the lipid content of the sera in these individuals. Thus LONGSWORTH et al. did not determine the distribution of different lipoproteins. Readers interested in a more detailed survey of the literature on lipoproteins are referred to NIKKILÄ (1953), SWAHL (1953) and TULLIS (1953).

Ultracentrifugal determinations of the concentration of certain lipoprotein molecules (S_f 10—20 class) were reported by KEMPE et al. (1952) for 147 children ranging in age from birth to 15 years. The lipoprotein values present in serum from umbilical cord blood (in 51 newborn infants) were of the same order as those found in the total group of children and were almost the same as those for

normal women aged 21—30 years. The marked increase in serum lipids during the neonatal period is thus not reflected in the S_f 10—20 class lipoproteins.

RAFSTEDT & SWAHL (1954) determined not only the total and free cholesterol, phospholipids and total lipids, but also the lipoproteins in umbilical cord blood and in capillary blood of infants 1—6 days old. The marked increase in the serum lipids after birth was ascribable above all to the striking increase in the β -lipoproteins. An increase was also observed in the α -lipoproteins. On determination of the protein fractions by means of electrophoresis on filter paper it was also found that during the first few days of life the α_2 - and β -globulins showed a statistically significant increase and γ -globulin a statistically significant decrease. The albumin fraction did not change significantly.

COMMENTS

It is apparent from the survey of the literature that it has not been possible to determine normal values of serum lipids for infants with certainty. Owing to the differences in the methods used, it is difficult to compare the values of the various series on record. None of the investigators have performed a complete investigation of the serum lipids including total lipids, total and free cholesterol and phospholipids. It seems established that the serum lipid values at birth are low and that they increase during the first few days of life, but by no means to adult level. The course of the following increase up to adult levels has not been cleared up properly. While some authors believe that the lipid values reach the normal adult level already in the second month of life, others claim that the increase is gradual and continuous throughout childhood. However, with modern analytical methods it seems to have been claimed that after the first year of life the lipids do not increase with increasing age with certainty, even though the individual values vary widely. The contradictory reports about the increase with age in adults show how difficult it is to form a clear opinion of the serum lipid values even in adults.

As to the lipoproteins, it is evident from the survey of the litera-

ture that our knowledge about lipoprotein distribution in childhood is scanty. The S_f 10—20 class lipoproteins represent only a part of the lipoproteins and are not correlated with certainty with the lipoproteins separated by electrophoresis.

The investigation of RAFSTEDT & SWAHLN (1954) showed that the marked increase in the serum lipids during the first few days of life is ascribable above all to the striking increase in the β -lipoproteins, but also to an increase in α -lipoproteins and "start"-fraction. However, in the neonatal period neither the serum lipoproteins nor the serum lipids have reached normal adult values. It was therefore considered worth while to investigate the further changes in the serum lipids and lipoproteins and the age at which these values reach normal adult level.

Table 1. A survey of the most important lipid analyses in infants and children.

Age	Authors	Number of cases	Total lipids	Phospholipids	Total cholesterol	Ester cholesterol	Free cholesterol
At birth							
1912	HEERMANN & NEUMANN	?	436	207	98	75	23
" "	SLEMONS & CURTIS	10			115—225		
" "	1921 ROSENTHAL & MEIFER	7			57(42—66)		
" "	1923 PLASS & TOMKINS	11		107			
" "	1923 SLEMONS & STANDER	7	736(665—790)	225(200—240)	148(125—185)		
" "	1926 HORNING	?			62		
" "	1924 GYÖRGY	6		95	69		
" "	1926 —	14		103	80		
" "	1926 HELLMUTH	30	660	110	70		
" "	1928 GORDON & COHN	16		103	89		
" "	1936 BOYD	29	198(97—367)	61(21—166)	34(17—86)	20(0—57)	14(6—29)
" "	1936 SPERRY	6			61		
" "	1937 SINN & MCNAMARA	24	221(119—331)	27(0—94)	80(55—120)	48(28—76)	32(23—44)
" "	1954 RAFSTEDT & SWAHLN	50	347(120—600)	75(48—133)	75(50—110)	53(28—81)	22(13—34)
" "	1955 RAFSTEDT	15	313(170—440)	124(76—170)	74(48—98)	48(36—67)	26(19—38)
3 days	1926 HORNING	?			80	33	47
5—7 days	1926 —	?			90	51	39
1st month	1926 GYÖRGY	10		155	124		
1st week	1928 GORDON & COHN	16		105	87		
1—25 days	1936 SPERRY	63			133(71—190)	86(36—126)	46(25—61)
6—10	1937 SINN & MCNAMARA	25	468(297—651)	103(19—190)	135(108—179)	84(61—112)	51(37—68)
1—6	1954 RAFSTEDT & SWAHLN	50	591(340—890)	131(70—178)	138(98—200)	88(37—137)	50(25—105)
3—10	1955 RAFSTEDT	15	608(130—760)	207(160—260)	134(110—167)	86(58—119)	49(37—59)
1—4 months	1926 GYÖRGY	30		158	134		
4—12	1926 —	24		162	159		

Age		Authors	Number of cases	Total lipids	Phospho-lipids	Total cholesterol	Ester cholesterol	Free cholesterol
1—1 months		1927 MANICATIDE et al.	24			131		
1—12 "		1927 —	24			116		
1—12 "		1928 BAYLAC & SENDRAIL	20			95—120		
5—12 "		1928 GORDON & COHN	6			136(110—180)		
1—12 "		1931 KUGELMASS & GREENWALD	11			164(142—206)		
1—6 "		1937 HANSEN	6	494(385—662)		164(142—206)		
6—12 "		1937 —	11	503(417—643)		179(128—232)		
2—9 "		1940 RADWIN et al.	3	691(520—848)	180(138—212)	165(139—198)		
2—6 "		1943 HODGES et al.	16			200		
7—12 "		1943 —	27			206		
1—12 "		1955 RAESTEDT	37	606(240—850)	188(122—276)	130(69—173)		
2—6 years		1926 GYÖRGY	4		196(170—235)	173(144—181)		
6—13 "		1926 —	9		205(172—225)	190(150—250)		
1—2 "		1928 GORDON & COHN	9			141		
2—6 "		1928 —	23			162		
1—2 "		1928 BAYLAC & SENDRAIL	11			143		
2—5 "		1928 —	20			153		
5—10 "		1928 —	26			161		
10—15 "		1928 —	23			169		
3—12 "		1936 OFFENKRANTZ & KARSHAN	107			183		
1—2 "		1937 HANSEN	4	539(468—639)		168(150—200)		
2—15 "		1937 —	28	558(326—662)		199(160—281)		
1—6 "		1940 RADWIN et al.	11	651	190	233		
6—16 "		1940 —	40	600	170	186		
2—13 "		1943 HODGES et al.	417			194—220		
6—14 "		1947 THOMAS	24	620(480—755)	190(135—265)	210(130—275)	140(75—255)	70(40—140)
1—16 "		1948 KORNFRUP	95	820(390—1155)	195(135—295)	209(132—299)	152(93—226)	57(37—84)
1—6 "		1952 WAMBERG	119	804(470—1350)	196(103—317)	182(79—310)	127(49—230)	55(25—132)
2—14 "		1955 RAESTEDT	25	838(190—1090)	235(188—292)	188(138—212)	134(99—161)	54(39—69)

CHAPTER III

METHODS

A quantity of 0.6 ml serum was sufficient for the performance of the following determinations.

1. Determination of total lipids (0.02 ml serum).
2. Determination of the relative concentrations of lipids in electrophoretically separated lipoprotein fractions (0.02—0.03 ml serum).
3. Determination of total and free cholesterol | (0.5 ml serum).
4. Determination of lipid phosphorus |

As the micromethod for the determination of lipid phosphorus is a new modification of the macromethod described by POSBORG PETERSEN (1952) it is described in detail below. The other methods are only described in brief, and readers interested in details are referred to the original descriptions.

QUANTITATIVE DETERMINATION OF TOTAL AND FREE CHOLESTEROL

The determinations were made by the method of SCHOENHEIMER & SPERRY (1934). A quantity of 0.5 ml serum was extracted with 10 ml of boiling ethanol and acetone in equal parts. The extract was filtered through a fat-free filter, and the following quantities of the extract were used for the various determinations: 1 ml for the determination of total cholesterol, 2 ml for the determination of free cholesterol and 4 ml for the determination of lipid phosphorus.

For the determination of the total cholesterol the combined cholesterol was hydrolysed by the addition of KOH. After hydrolysis the solution was titrated with HCl, phenolphthalein being used as indicator. Addition of digitonin solution gives a precipitation of cholesterol as cholesterol digitonide. After centrifugation and wash-

ing of the cholesterol digitonide the latter was dried and dissolved in concentrated acetic acid. The colorimetric analysis according to LIEBERMANN-BURCHARD was carried out with a Beckman spectrophotometer at 610μ in a 1 cm cuvette.

The free cholesterol was determined in the same way as the total cholesterol with the exception of hydrolysis.

The error of the method ($=s$) was studied by statistical analysis of the values obtained from 25 double determinations (i.e. double test performed on different sera). The following formula was used:

$$s = \sqrt{\frac{\sum d^2}{2n}}$$

Here d denotes the difference between the values obtained from the double determination and n the number of pairs.

The error of the method was for total cholesterol as below:

Observations below 100 mg per 100 ml	1.8
" 100—199 " " 100 "	2.1
" above 200 " " 100 "	3.0

The mean error for free cholesterol:

Observations below 50 mg per 100 ml	0.8
" above 50 " " 100 "	1.1

It was found that s slightly increased with increasing values estimated.

DETERMINATION OF TOTAL SERUM LIPIDS

Quantitative determination of the total serum lipids was performed by SWAHLN's micromethod (1952 and 1953). As test lipid use was made of a normal serum, the total lipid content of which had been determined by BRUN's (1939) method.

The method is based on the deposition of a drop of serum on filter paper and subsequent colouring of the lipids with a solution of Sudan black in 50—55 per cent ethanol. The colour taken up by the lipids is directly proportional to the concentration of the total lipids in the serum.

The saturated solution of Sudan black was prepared as follows: About 0.1 gm Sudan black was added to 100 ml of 60 per cent ethanol. The mixture was stirred continuously during heating to boiling point. It was then

allowed to stand over night in a stoppered flask, during which undissolved particles sedimented. Then the mixture was filtered (Munktell No. 00 filter paper) at least twice to separate off undissolved particles of Sudan black.

The method may be briefly described as follows: Small incisions 1.5 cm apart are made along the longitudinal edge of a filter paper (Whatman No. 1) measuring 4 cm by 26 cm. With the aid of a micropipette 0.02 ml serum is placed in the middle of each field. One field in the middle and the fields at either end of the filter paper are left free and used as blanks. In two of the fields 0.02 ml of the test serum is also placed. Five double determinations can be made on a single filter paper. When depositing the spot of serum on the paper, the latter should be held at either end, so that it does not come into contact with any underlying surface. The serum spots on the filter paper are allowed to dry in the air. The filter paper is then placed in a bath consisting of saturated Sudan black solution, where it remains for three hours. The paper is afterwards washed in 100 ml of 50 per cent ethanol in three baths, 15 minutes in each bath. The filter paper is allowed to dry in the air and is then cut into segments at the sites of the incisions along the longitudinal edge of the paper. The colour taken up by each serum spot is then eluted with 20 volume per cent acetic acid in absolute ethanol. The extinction value of the solution is read against ethanol-acetic acid in a Beckman spectrophotometer in a 1 cm cuvette at 590 μ .

The amount of total lipids is determined by subtracting the extinction value for the blank from that for the serum spots. The amount of total lipids in serum is determined in milligrams per 100 ml by the following formula:

$$\frac{\text{Lipid content (mg/100 ml) of test serum}}{\text{Ext. value for test serum}} \times \text{Ext. value for serum spot.}$$

The error of the method ($= s$) was studied by a statistical analysis of the values obtained from 110 double determinations. The following formula was used:

$$s = \sqrt{\frac{\sum d^2}{2n}}$$

Here d denotes the difference between the values obtained from the double determination and n the number of pairs.

The following values of the error of the method were found:

Observations below 299 mg per cent	8
" 300—499 " " "	9
" 500—699 " " "	14
" above 700 " " "	12

It is to be pointed out that the double determinations have been placed beside each other on the same paper and thus also coloured in the same Sudan black solution.

Sera from normal adults were used as test lipids. The total lipids in these sera were determined by BRUN's (1939) method. The total lipid content in these sera was selected to be about 600—700 mg per 100 ml. Using the same formula as above, the error of the method was found to be 24 units (mg/100 ml).

DETERMINATION OF THE RELATIVE CONCENTRATIONS OF LIPIDS IN ELECTROPHORETICALLY SEPARATED LIPOPROTEIN FRACTIONS

I. TECHNIQUE FOR ELECTROPHORETIC SEPARATION AND COLOURING OF THE LIPOPROTEINS

A slight modification of the micromethod described by SWAHLN (1952 and 1953) was employed.

The method is based on the electrophoretic separation of serum lipoprotein components and subsequent colouring of the separated lipoproteins with the solution of Sudan black in 50—55 per cent ethanol. The electrophoretic separation is carried out on filter paper according to the method described by KUNKEL & TISELIUS (1951). The apparatus described by KÖIW, WALLENIUS & GRÖNWALL was used.

On account of the low lipid content of umbilical cord blood, 0.03 ml serum was used for the electrophoretic separation. In the other samples 0.02 ml serum was used. The electrophoretic separation was interrupted after 4½ hours. The filter paper was then dried at 80° C in a thermostat. The serum lipids on the filter paper were coloured in the same way as that described for colouring total lipids by SWAHLN's micromethod.

For elution of the colour in the different lipoprotein fractions, the filter paper was cut into 10 mm transverse sections. The colour in these sections was eluted for 30—60 minutes with 20 per cent acetic acid in absolute ethanol. The extinction values were read in a Beck-

man spectrophotometer with the use of a 1 cm cuvette at 590 μ . The eluate of a lipid-free segment of the strip of paper used for the electrophoretic separation was taken as a blank.

2. EVALUATION OF THE SEPARATED LIPID FRACTIONS

Figs. 1 a and b show the result of colouring lipoproteins in serum after electrophoretic separation in filter paper. In Figs. 2 and 3 the lipoprotein distribution in the same sera is given in relation to the protein fractions. The lipoprotein zone that had migrated farthest is located in the α_1 -globulin and albumin region. A faintly coloured, irregular zone is seen in the position of the α_2 -globulin. In the position of the β -globulin fraction there is another distinctly coloured zone, which fades towards the starting point of the electrophoretic boundary. At the starting line there is another zone, which is not distinctly separated from the β -lipoprotein fraction. In the calculation of the distribution per cent of the various lipoprotein fractions, the fraction at the starting line was taken as a segment 5 mm on either side of the starting line. As the α_2 -lipoprotein fraction was inconstant, it was included in the α_1 -lipoprotein fraction, hereinafter called α -lipoprotein.¹

In order to check the accuracy of the method 10 samples of one and the same serum were fractionated, and the results were analysed statistically by the methods given below.

Ten determinations of one and the same serum were made for determining the percentage distribution of the different lipoprotein fractions.

For determination of the error of the method the following formula was used:

$$\varepsilon = \sqrt{\frac{\sum (x - m)^2}{n-1}}$$

¹ After the present investigation was finished, it was found (LAURELL, unpublished) that it is possible to separate the α -lipoprotein fraction analysed in this investigation into two fractions, one with the same mobility as albumin and one with the same mobility as the α_1 -lipoprotein isolated by COHN's ethanol fractionation method. Using the technique devised by LAURELL it was found by the writer, that these two fractions are present in serum from umbilical cord blood as well as in serum from infants and children.

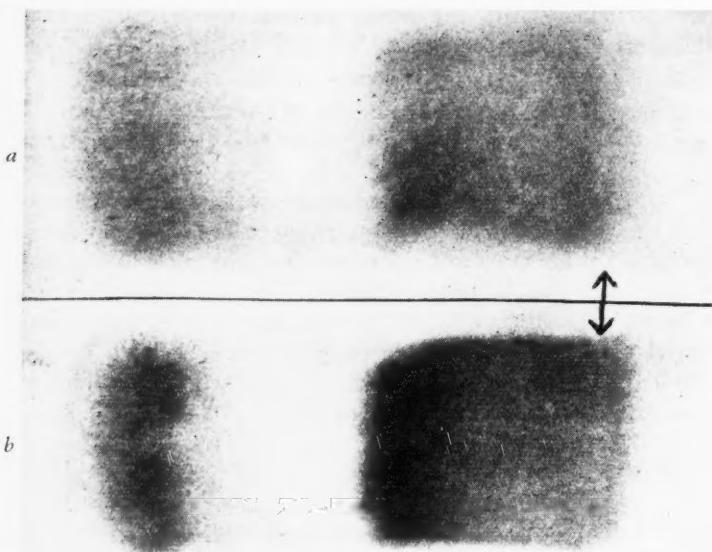


Fig. 1. *a* represents the result of colouring lipoproteins in serum from umbilical cord blood after electrophoretic separation in filter paper. The arrow indicates the starting line. — *b* represents the lipoprotein distribution in serum from the same infant six days after birth.

The α -lipoproteins have migrated farthest. In the position of the β -globulin fraction is another distinctly coloured zone, β -lipoproteins, which fades towards the starting line. As seen in Fig. 1 *a*, the β -lipoprotein zone is much fainter and less well defined in serum from cord blood than in serum from the same infant six days old (Fig. 1 *b*). At the starting line is another zone, start fraction, which is not distinctly separated from the β -lipoprotein fraction.

Here m is the mean value of all the determinations and n the number of observations, in this case 10.

The following values are found:

Fraction	Number of observations	Mean value	$\Sigma (x - m)^2$	The error of the method
α	10	27.6 per cent	14.4	1.3
β	10	50.6 " "	20.4	1.5
Start	10	21.8 " "	25.6	1.7

DETERMINATION OF TOTAL PHOSPHOLIPIDS

A micromethod was devised which permits determination of the total phospholipids in 0.2 ml serum. The method is based on the investigations of EGSGAARD and POSBORG PETERSEN.

INTRODUCTION

The purpose of extraction of phospholipids is to isolate them in a suitable solvent so that they can afterwards be determined by analysis of the ashed extract, in other words, the quantitative transfer of the phospholipids from serum to the solvent, but without the transfer of other substances containing phosphorus. According to BRUN (1939), the primary lipid extract should be purified because of the possibility of its being contaminated with phosphorus substance other than phospholipids. She therefore re-extracted the dried primary lipid extract in petroleum ether. EGSGAARD, however, found that despite careful precautions, there is a loss of the phospholipids on re-solution in petroleum ether. He also showed that inorganic phosphorus is not extracted with alcohol. He therefore concluded that re-solution in petroleum ether is both unnecessary and inadvisable. POSBORG PETERSEN claimed that the relatively low phospholipid values obtained by the method of BRUN are probably ascribable to loss on re-solution of the evaporated dry primary lipid extract in petroleum ether. In the determination of phospholipids POSBORG PETERSEN uses 20 ml of filtered alcohol-acetone extract, corresponding to 1 ml serum. This is transferred to a Kjeldahl flask. The lipid extract is evaporated and is ashed in accordance with NEUMANN (1902). The contents of the flask are then transferred to a 25 ml volumetric flask by repeated rinsing with distilled water before the colorimetric determination is performed.

When trying to work out a suitable micromethod the present writer found that not only the re-solution of the primary lipid extract in petroleum ether but also its transfer from one flask to another causes considerable errors in the values obtained for phospholipids as compared with the macromethods of BRUN and POSBORG PETERSEN. In order to prevent losses during transport, the

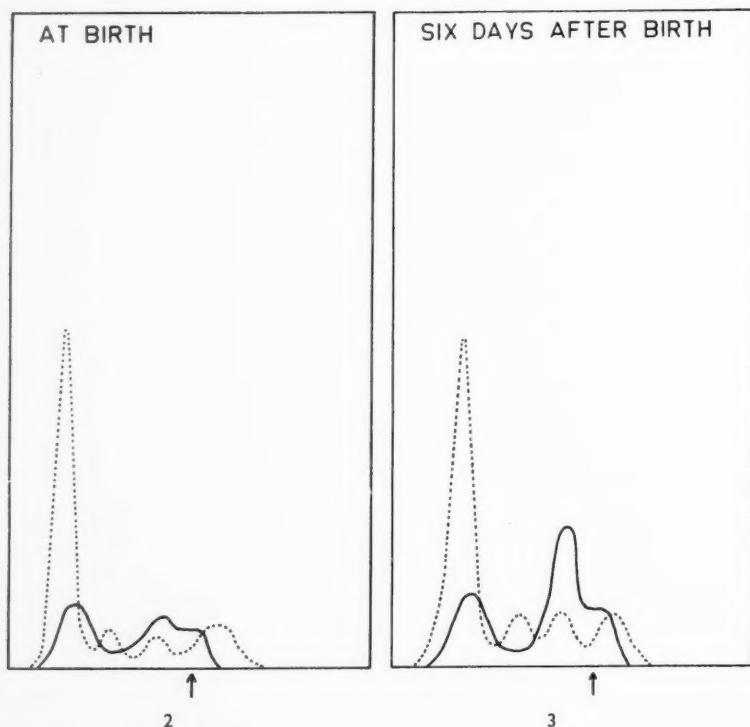


Fig. 2. Diagram showing the separate protein (dotted line) and lipid (solid line) components of umbilical cord blood. The starting point is marked by an arrow.

Fig. 3. Diagram showing the separate lipid and protein components in serum from the same infant as in Fig. 2, six days after birth. For comparison with normal adult, see Fig. 4 on page 23.

primary lipid extract was placed in a combustion tube, which was also used as a measuring cylinder with suitable graduation. It was found that a combustion tube of pyrex glass, 180 mm by 18 mm, and graduated in 10 ml was most suitable.

PROCEDURE. — A quantity of 0.5 ml serum is extracted with 10 ml boiling alcohol-acetone ad modum SCHOENHEIMER & SPERRY

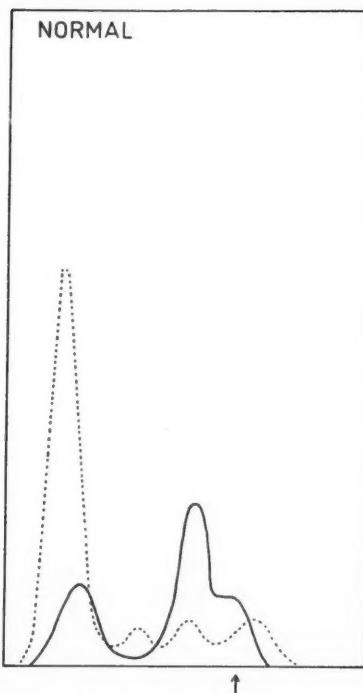


Fig. 4. Diagram showing the separate lipid and protein components in serum from normal adult.

and then filtered. 4 ml of the lipid extract is transferred in the above-mentioned combustion tube and evaporated in a thermostat at 90° C (1 ml and 2 ml, respectively, of the lipid extract is used for determination of total and free cholesterol). The lipids are ashed wet with 0.2 ml concentrated sulphuric acid and 0.2 ml concentrated nitric acid. The nitrous gases are allowed to escape, after which the mixture is boiled for a further 10 minutes over gentle heat, so that the white sulphuric acid gas is not forced out of the tube. By fixing the tube at 45 degrees this procedure is not difficult. The ashed material is then diluted to a volume of 10 ml in the graduated combustion tube with the aid of distilled water. Of this, 4 ml are transferred to a test tube, to which 2 ml amidol-sulphite and 2 ml molybdate solution are then added. After 30 minutes the intensity of the blue colour that develops is read in a Beckman spectrophotometer

at 720 μ in a 1 cm cuvette. The lipid phosphorus value multiplied by the factor 25 gives the concentration of the total phospholipids in milligrams per 100 ml.

CONTROLS. — In order to form an opinion of the accuracy of the method it was compared with the macromethods of BRUN and POSBORG PETERSEN.

Lipid phosphorus in mg/100 ml serum

Samples	Micromethod				Posborg Petersen's method	
Serum 1	9.12	9.20	9.20	9.28	9.20	9.28
Serum 2	11.76	11.68	11.68	12.08	11.84	11.84

As is apparent, good agreement was found between the results of this micromethod and those of POSBORG PETERSEN's macromethod. The means for the micromethod and macromethod were 9.20 and 9.24 mg/100 ml for one serum and 11.80 and 11.84 mg/100 ml for the second serum.

Lipid phosphorus in mg/100 ml serum

Samples	Micromethod	Brun's method
Serum 1	8.6	8.0
Serum 2	13.0	11.9
Serum 3	16.6	16.6
Serum 4	12.4	12.2
Serum 5	7.2	6.1

The above results of the analysis by the two methods are based on double determinations. It is apparent that there is a tendency to lower values by BRUN's method as compared with the present micro-method. This may be explained by the loss of lipids on re-solution of the evaporated dry lipid extract in petroleum ether.

The error of the method ($=s$) was studied by a statistical analysis of the values obtained from 30 double determinations. The same formula was used as for total cholesterol and free cholesterol.

It was found that s slightly increased with increasing values estimated. Thus s for values below 6.00 mg per 100 ml was found to be 9.1 hundredths and for values above 6.00 mg per 100 ml 15.4 hundredths. For all the observations the mean error was found to be 12.2 hundredths.

SAMPLING TECHNIQUE

Umbilical cord blood was collected in the following way: Immediately after birth the cord was clamped by two forceps placed close to one another and then the cord was divided between them. The placental stump of umbilical cord was afterwards held over a centrifuge tube. The forceps was then opened and blood from the cord was allowed to flow spontaneously into the centrifuge tube. The blood was stored in the cold for at least one hour before centrifugation and removal of the serum.

Capillary blood was collected from the tip of a finger. In order to avoid vasoconstriction, which makes collection of the blood from newborns difficult, the hand was first massaged and placed a few minutes in warm water. After the tip of the finger had been cleaned with ether, two small incisions were made in the tip of the finger by means of a sharp stilette. Blood was then collected with the aid of a Pasteur pipette and transferred to a centrifuge tube. After the blood had been allowed to stand for at least one hour for retraction of the clot, it was centrifuged and the serum was pipetted off.

The serum samples were kept in small sealed tubes in the cold ($+4^{\circ} \text{ C}$) until analysed. As a rule, the samples were analysed within one week after collection.

All the blood samples in this work were taken in the post-absorptive state, i. e. in the morning before the first meal. The infants and children had then been fasting for at least 8 hours.

As a rule, the samples were analysed within one week after collection. In twins and in those cases in which two determinations were made at short intervals, e. g. during the first week of life, these samples were analysed simultaneously. The total lipids were determined on the same paper and the electrophoretic separation on filter paper was performed in parallel.

CHAPTER IV

SERUM LIPIDS AND LIPOPROTEINS IN FULLTERM NEWBORNS DURING THE FIRST FEW DAYS OF LIFE

As mentioned earlier, the serum lipids are low at birth and increase remarkably during the first week of life (see Table 1). Thus HORNUNG (1926) showed that the total serum cholesterol increased from 62 mg/100 ml at birth to 90 mg/100 ml 5—7 days later. SPERRY (1936) found a more marked increase of total cholesterol during the first days of life, e. g. from 61 mg/100 ml at birth to about 130 mg/100 ml 3—4 days later. He also noted that the total cholesterol persisted at this level during the rest of the first month of life. SENN & McNAMARA found an increase in total cholesterol from 80 mg/100 ml to 135 mg/100 ml as well as a corresponding marked increase in the total lipids and phospholipids during the first 6—10 days of life. RAFSTEDT & SWAHL (1954) confirmed this marked increase in serum lipids during the first 6 days of life. They also studied the distribution of the lipoproteins during that time and found the increase in the β -lipoproteins to be mainly responsible for the increase in the serum lipids.

MATERIAL

In order to form a clearer opinion of the increase during the first hours and days after birth an analysis was made of specimens from 30 fullterm infants to healthy mothers. Pregnancy and delivery had been uncomplicated throughout. Blood samples were collected from all the infants at birth (umbilical cord blood). Thereafter one or two blood samples were collected from the same infants at different intervals, e. g. 1—13 hours after birth before the intake of the first meal, and 1—10 days after birth. In most cases the infants received

breast milk only, in some cases breast milk and citrido milk¹ and in one case citrido milk only.

Two healthy fullterm infants were delivered by Caesarian section and blood samples were taken in the same manner from these infants as from the other infants.

RESULTS

Tables 2 and 3 give the results of the analysis of serum lipids (32 cases) and serum lipoproteins (30 cases). The mean value, the mean error and the range of the various serum lipids and lipoproteins in the umbilical cord blood are also given at the end of the tables.² The scatter of the total lipid, total cholesterol and phospholipid values was so great as to render the arithmetic mean of the group valueless as representing the behaviour of the individuals.

In order to form an opinion of the increase in serum lipids after birth, the first question to receive attention was whether a high lipid value in the umbilical cord blood might be accompanied by a smaller increase after birth than a low lipid value in the umbilical cord. In an attempt to find an answer to this question those fullterm and premature infants, from whom specimens had been collected on day 4, day 5, day 6, day 7 and day 8 were selected. (See Tables 2, 8 and 10.) The fullterm and premature infants were divided into two groups according to the level of the determinations in serum from cord blood.

Group	Number of cases	Mean increase (mg 100 ml) in	
		total lipids	total cholesterol
1. Low initial values	11	2.13	60.5
2. High initial values	11	235	55.5

¹ Citric acid milk prepared with cow's milk containing 3 per cent fat.

² The standard deviation (*S.D.*) was derived by the following formula:

$$S.D. = \sqrt{\frac{\sum (x - M_x)^2}{n-1}}$$

The mean error (ε) was derived by the following formula:

$$\varepsilon = \frac{S.D.}{\sqrt{n}}$$

In view of the wide individual variation, the difference between the means given above is of no importance. Thus, as no definite relation was found between the initial value and the order of the increase, the latter may be regarded statistically as an independent factor.

In 17 cases the level of the serum lipids was determined both in umbilical cord blood and capillary blood taken 1—13 hours after birth and before the infants had received their first meal. The mean increase of serum lipids during this time was as follows:

Time	Number of cases	Mean increase (mg 100 ml) in		
		total lipids	total cholesterol	phospholipids
1—13 hours	17	38	5.4	12.7
1—6 "	9	42	4.8	12.4
7—12 "	7	34	6.3	11.7
13 "	1	30	5	22

It is thus apparent that the total lipids, total cholesterol and phospholipids increased before the intake of the first meal. This increase did not vary in size with the time between birth and collection of the second sample.

In 11 infants the serum lipids were studied both in umbilical cord blood and in capillary blood after the first meals 19—38 hours after birth. Six of the infants received in addition to breast milk supplementary citrido milk varying in total amount between 20 and 30 grams during 18—24 hours after birth. The other 5 infants were only breast fed during 34—38 hours after birth. The increase of the serum lipids from birth was as follows:

Group	No. of cases	Average time in hours	Mean increase (mg 100 ml) in		
			total lipids	total cholesterol	phospholipids
Citrido milk + breast milk	6	22	130	25	51
Breast milk only	5	36	244	32	72

As is apparent, the serum lipids increased with time after birth. The addition of citrido milk did not seem to accelerate the increase.

As mentioned earlier, SPERRY showed that the total cholesterol in serum increases rapidly during the first 3—4 days of life and after-

wards persists at the same level throughout the first month of life without any tendency to increase or decrease. This is illustrated by case No. 2 not only concerning total cholesterol, but also concerning the total lipids and phospholipids. After a rapid increase for the first four days of life all the serum lipids showed the same level 24 days later.

In order to elucidate the maximal increase of the serum lipids during the first 3—4 days, in 15 cases blood specimens were taken from umbilical cord blood and from capillary blood 3—10 days later. In 14 cases the capillary blood was taken on the third to sixth day of life and in one case on the tenth. The increase of total lipids, total cholesterol and phospholipids is given in the compilation below together with the values for the increases of the serum lipids earlier mentioned in this chapter.

Time	Mean increase (mg 100 ml) in		
	total lipids	total cholesterol	phospholipids
1—13 hours (fasting)	38	5.4	12.7
18—24 "	130	25	51
34—38 "	244	32	72
3—10 days	296	60	90

As is seen from the compilation above there is a gradual increase of serum lipids during the first few days of life. Below the mean values and variation ranges for serum lipids and lipoproteins in cord blood as well as in capillary blood 3—10 days later in the same 15 infants are summarised. The increase of total lipids, total cholesterol and phospholipids is about 80—90 per cent on an average. The remarkable increase of the serum lipids is shown in Fig. 5.

Serum lipids and lipoproteins in 15 newborn infants

Mg 100 ml	Cord blood		Capillary blood 3—10 days after birth	
	Mean value	Range	Mean value	Range
Total lipids	313±14	170—440	608±30	430—760
Total cholesterol	7.4± 3.5	4.8— 9.8	13.4± 4.9	11.0—16.7
Esterified cholesterol	4.8± 2.5	3.6— 6.7	8.6± 4.7	5.8—11.9
Free cholesterol	2.6± 1.4	1.9— 3.8	4.9± 1.5	3.7— 5.9
Phospholipids	12.4± 6.7	7.6—17.0	20.7± 8.1	16.0—26.0
α -lipoprotein	13.4± 9.0	7.1—17.6	19.4± 12	11.6—26.6
β -lipoprotein	10.3± 7.2	5.1—15.8	27.7± 11.5	21.5—32.0
"Start"-fraction	7.7± 4.9	4.8—10.6	13.8± 7.4	8.4—19.0

As is apparent from the compilation above, both the combined and free cholesterol increased during the first few days of life. The ratio between combined and free cholesterol — which, according to SPERRY, fluctuates within narrow limits (2.3 to 3.1) — in umbilical cord blood showed lower values throughout with a variation of 1.29 to 2.32 and a mean of 1.85. The next few days of life no remarkable change occurred in this ratio. The variation during third to tenth day post partum was 1.2 to 2.53 with a mean of 1.79. In other

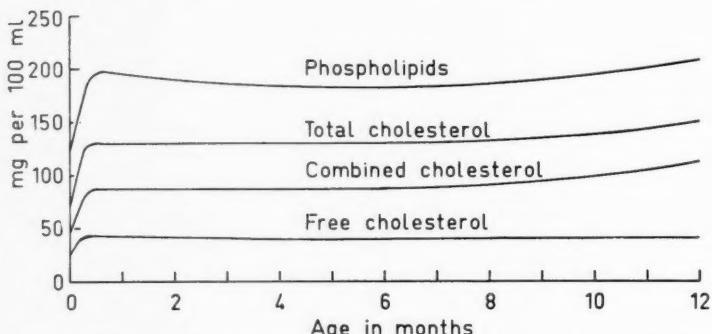


Fig. 5. Diagram showing the quantitative distribution of phospholipids, total, free and combined cholesterol from birth until the end of the first year of life.

words, combined cholesterol at birth represents on the average the same as a few days later, or about 65 per cent.

The cholesterol-phospholipid quotient, which in the adult is about 0.90, is also of interest. At birth this quotient for umbilical cord blood is 0.60 and a few days later 0.65 on the average.

The lipoproteins also show changes during the first few days of life. Table 3 shows the lipoprotein distribution for 30 fullterm infants during the first few days of life. Fig. 6 shows the marked increase of the lipoproteins during these days. The compilation above gives the means and ranges for 15 infants at birth and 3—10 days later. The increase in lipoproteins is also apparent from Figs. 1, 2 and 3. It is apparent that the most remarkable increase was that of the β -lipoprotein fraction, but also the α -lipoprotein and start-lipoprotein

fractions show a distinct increase. The distribution percentage of the various lipoprotein fractions at different times during the first few days of life is summarised in the compilation below:

Age	Number of cases	Distribution per cent of		
		α -lipopro- teins	β -lipopro- teins	"Start"- fraction
At birth	15	43	33	24
1—13 hours	17	42	31	27
18—24 "	6	36	38	26
34—36 "	5	31	42	27
3—10 days	15	29	46	25

It is apparent from the compilation above that no appreciable change occurs during the first hours of life before the first meal. Then the change occurs successively, and already 2—3 days after birth the distribution seems to have been roughly the same as that found in normal adults.

None of the data studied appeared to vary with sex or body weight at birth.

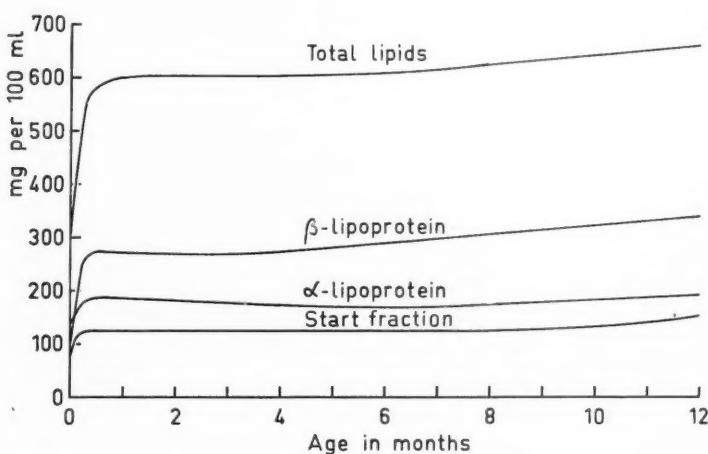


Fig. 6. Diagram showing the quantitative distribution of total lipids, α -lipoproteins, β -lipoproteins and start fraction from birth until the end of the first year of life.

The values found for infants delivered by Caesarian section were not found to differ from the values found for infants delivered by the normal route.

COMMENTS

A survey of earlier investigations of serum lipids from umbilical cord blood and from blood collected during the neonatal period is given in tabular form (Table 1). Of the later investigators of serum lipids in umbilical cord blood, BOYD (1936) reported values, which were lower than those found by any of the other investigators. BOYD himself pointed out that "oxalated blood gives lower values for lipids in the plasma than does heparinised or defibrinated blood". SPERRY & SCHOENHEIMER (1935) also showed that serum and heparinised plasma contain one and the same amount of cholesterol, while oxalated plasma contains much less. Judging by the wide range of the serum lipid values, one would expect the mean values in two materials to be different, even if the same method is used. As seen in Table 1, SPERRY found a lower mean value for total cholesterol in umbilical cord blood in 7 cases than that found for 15 cases in the present investigation. However, the increase in total cholesterol found by SPERRY during the first 3—4 days of life was 76 per cent, as against 81 per cent in the present material during the first 3—10 days of life. SPERRY did not determine the free cholesterol in serum from umbilical cord blood. In the present investigation the ratio between combined and free cholesterol varied from 1.3 to 2.3 in umbilical cord blood and from 1.2 to 2.5 some days later. In the 4—25 days old infants SPERRY found the same ratio to vary between 0.7 and 2.6. Thus, as in SPERRY's investigation it was found that the ratio between combined and free cholesterol during the neonatal period is lower than in adults (2.3—3.1).

SENN & McNAMARA carried out their investigation in the neonatal period by means of the gasometric micromethods of KIRK, PAGE & VAN SLYKE. As is apparent from Table 1, they collected specimens from the infants 1—13 hours after birth and then again 6—10 days later. As the present investigation shows that the increase of the lipid values the first few hours after birth is relatively

small, the results found by SENN & McNAMARA are comparable to those in the present investigation. As is apparent from Table 1, the serum lipid values found by them showed a wide variation range, as in the present investigation. They also found a marked increase of all the serum lipids during the first 6—10 days of life of the same order as in the present investigation. In SENN & McNAMARA's investigation, however, the phospholipids showed low values. In 3 of the children no phospholipids were demonstrable in the serum at birth and the variation range was 0—94 mg/100 ml with 27 mg/100 ml on the average. GYÖRGY, HELLMUTH, GORDON & COHN found the phospholipid value to be about 100 mg/100 ml in serum from umbilical cord blood.

In the investigation by RAFSTEDT & SWAHL the values for phospholipids were lower than in the present investigation. The method used by RAFSTEDT & SWAHL was a modification of BRUN's method. On closer control of this modification it was found that losses occurred during the performance of the analyses. Another micromethod was therefore worked out and employed in the present investigation. (See method chapter.)

As mentioned in the method chapter, the α_2 -lipoprotein fraction was not separated, because it was inconstant. It was therefore included in the α_1 -lipoprotein fraction. Addition of the α_1 - and α_2 -lipoprotein fraction in the investigation carried out by RAFSTEDT & SWAHL gave about the same value as for the α -lipoprotein fraction in the present investigation. The other lipoprotein fractions gave about the same mean values and ranges as in the present investigation.

The investigation carried out by LONGSWORTH et al. of the total lipid content in a fraction consisting of α_2 - and β -globulin in serum from umbilical cord blood is not strictly comparable with the lipoprotein studies carried out in the present investigation. LONGSWORTH et al. only showed that the total lipids in this fraction were smaller than the total lipids in the same fraction in serum from normal adults.

The investigation of S_f 10—20 class lipoproteins by KEMPE et al. is not either comparable with the lipoprotein studies in the present investigation. It is, however, of interest to note that in serum

from umbilical cord blood and from infants the levels of these lipoproteins were of the same order as those found for the entire group of children. It is obvious that the marked increase of lipoproteins found in the present investigation does not include S_f 10—20 class lipoproteins. It has been stated that S_f 3—8 class lipoproteins correspond to β -lipoproteins found by electrophoresis. S_f 10—20 class lipoproteins are not correlated with certainty with the lipoproteins separated by electrophoresis. The α -lipoproteins are not included in the method used by KEMPE et al., because their specific weight is higher than that of the salt solution (1.063) and are therefore forced to the bottom of the tube by the preparative centrifugation.

It has been stated in the present investigation that the serum lipids increased by about 10—15 per cent during the first hours after birth and before the intake of food. This increase did not vary with the time after birth. However, it has been stated that also other changes occur in the peripheral blood the first hours after birth. The closure of foramen ovale and the ductus arteriosus with the opening of the pulmonary circulation may play a role in this connection. WEGELIUS (1948) showed that the red blood cells in the peripheral blood of newborns increase from birth up to two hours after birth by about 9 per cent of the initial value. During this time the haemoglobin value, the haematocrit value and the white blood cell count increase by about the same amount. As she found that even total plasma protein increases during the first two hours after birth she concluded: "The probability that a dehydration of blood takes place with a great part of the newborn infants during the first post-natal hours is supported by the investigation." In the light of WEGELIUS's investigation, there is reason to suppose that the increase of the serum lipids during the first fasting hours after birth is a part of other changes in the peripheral blood during this time, it might possibly be due to a dehydration of blood.

SPERRY (1936) discussed whether the increase of the total cholesterol by 76 per cent during the first 3—4 days of life might be due to concentration of the blood plasma. He therefore investigated whether the total protein content increased in proportion to the total cholesterol content. When the corresponding values for these

two constituents of the plasma were plotted against each other, SPERRY found that there was no relation between them. Even if the total plasma protein does not continue to increase after the first hours of life, a change in the relative distribution of the protein fractions during the first few days of life has been shown by RAFSTEDT & SWAHLN (1954). They found that both α - and β -globulins showed a highly significant increase while the γ -fraction showed a highly significant decrease. The albumin fraction did not show any statistical changes. PFAU (1954), who also used paper electrophoresis, came to the same conclusion. Using TISELIUS's macroelectrophoresis MOORE, DU PAN & BUXTON (1949) also showed an increase of the α - and β -globulins as well as of the albumin fraction and a decrease of γ -globulin. They ether-extracted some samples of sera from cord blood and from adults by the method of MCFARLANE. The ether extraction resulted in a great diminution in the albumin fraction as well as in the β -globulin fraction. They drew no conclusions whether the change in protein distribution found by them during the first few days of life may be ascribed to an increase in the lipid content of serum. NIKKILÄ (1953) showed that after injection of heparin intravenously some material passed from β - to α -globulin in the TISELIUS pattern and that this alteration was caused by a transfer of lipids. It is of interest to note that the marked increase of serum lipids during the first week of life is accompanied not only by a change in the distribution of the lipoprotein fractions, but also by a change in the distribution of the protein fractions.

The investigations of SOULE (1939) and others have shown that estrogenic hormones are present in equal concentration in both the maternal and the fetal circulation. The presence of estrogenic hormones in marked concentration in the fetal circulation is consistent with the clinical observation of vernix caseosa, acne fetalis, enlarged breasts and bloody vaginal discharge in newborn infants. As there is no evidence that the fetus produces an excess of estrogenic hormones, it may be assumed that the placenta is permeable to estrogenic hormones. After birth and the cessation of placental transmission newborns excrete large amounts of estrogenic hormones. This has been shown by JAYLE & CRÉPY (1953), who found that

during the first 4 days of life the infant excreted in the urine a rapidly decreasing amount of estrogens, and on the fifth day of life no estrogens could be recovered from the urine.

That there is a correlation between the hormonal regulation and the lipoprotein distribution has been shown by RUSS, EDER & BARR (1951). They found that young women, 18—35 years old, have a greater percentage of their total plasma cholesterol in the α -lipoprotein fraction and correspondingly less in the β -lipoprotein fraction than men of corresponding ages. After the menopause this sex difference is no longer demonstrable. They therefore concluded that the estrogenic hormone can influence the distribution of lipoproteins. By giving estrogenic hormone to men who had survived myocardial infarction, they (BARR, RUSS & EDER, 1952) showed an increase in the amount of cholesterol in the α -lipoprotein fraction and a corresponding decrease in the β -lipoprotein fraction. The plasma total cholesterol also decreased progressively during the entire course of treatment. On cessation of estrogenic treatment there occurred an abrupt rise in the level of total cholesterol, a decrease in the percentage of cholesterol in the α -lipoprotein fraction and a corresponding increase of the percentage of the β -lipoprotein fraction. EILERT (1953) found that estrogens considerably decreased the cholesterol-phospholipid ratio.

It is of interest to note that during the first few days of life, when the excess of estrogen hormones is rapidly excreted by the infant, a similar change in the distribution of the lipoproteins occurs as is mentioned in the investigation with estrogenic hormone by BARR, RUSS & EDER.

At the same time as the serum lipids show a marked increase, the α -lipoproteins decrease from 43 per cent to 30 per cent, while the β -lipoproteins show a corresponding increase.

As far as is known, serum lipids do not occur in a free state but in combination with proteins in the form of lipoproteins. The composition and the properties of the lipoproteins are in keeping with the concept of their function as carriers for lipids. In various types of hyperlipemia the α -lipoprotein fraction remains remarkably steady, while the β -lipoprotein fraction shows a marked increase. The β -lipoproteins in hyperlipemia thus show the greater lipid bind-

ing capacity. The low β -lipoprotein fraction in serum from cord blood may suggest that its function as carrier for lipids is decreased in the fetus. During the first few days after birth there occurs a physiologic adaptation process, which is also reflected by a change in the distribution of the lipoproteins with a remarkable increase in the β -lipoprotein fraction. Even though the β -lipoproteins showed the greatest increase the first few days after birth, the α -lipoproteins also showed an increase suggesting the profound change occurring after birth. After the first week of life the lipoprotein distribution is relatively about the same as for normal adults, although the serum lipids are lower throughout.

SUMMARY

It was shown that the total lipids, total and free cholesterol as well as the phospholipids of serum from umbilical cord blood are much lower than in normal adults.

The investigation of lipoproteins in serum from umbilical cord blood showed that the α -lipoproteins represented about 43 per cent and the β -lipoproteins about 33 per cent. This ratio is likewise different from that found in normal adults, where the corresponding figures are about 30 per cent and 50 per cent.

During the first 12 hours of life the total lipids, total cholesterol and phospholipids increase by about 10—15 per cent. This increase does not vary with the time between birth and collection of the sample. It is suggested that this increase might be due to a dehydration of the blood during the first postnatal hours, during which no changes occur in the lipoprotein distribution.

During the first few days all the serum lipids increased steadily. Supplementary diet during the first day of life did not appear to accelerate the increase in serum lipids.

During the first few days of life the increase of the serum lipids was accompanied by a marked change in the ratio between the α - and β -lipoproteins. Thus on the fourth day the α -lipoproteins represented 29 per cent and the β -lipoproteins 46 per cent of the total lipids, a ratio corresponding roughly to that found in normal adults. Quantitatively, however, all the lipoproteins showed an absolute increase

during that time. The most marked increase was that of the β -lipoproteins which was more than 100 per cent.

It was shown that the ratio of the combined to free cholesterol, which in the adults varied within narrow limits (2.3—3.1), is much lower (1.3—2.3) in umbilical cord blood. During the first few days of life both the combined and the free cholesterol increase in absolute amount, but with no change of the ratio between them.

The cholesterol-phospholipid quotient, which is about 0.90 in adults is about 0.60 in umbilical cord blood and increases to about 0.65 during the first few days of life.

None of the data studied appeared to vary with sex or body weight at birth.

The values found for children delivered by Caesarian section were not found to differ from the values found for children delivered by the normal route.

Table 2. *Serum lipids in newborn full-term infants during the first days after birth*

Case No.	Sex	Age	Weight	Total lipids	Total cholesterol	Ester. cholesterol	Free cholesterol	Phospholipids	Remarks
5	M	At birth	2500	210	48	30	18	76	Breast milk
		8 hours		250	54	32	22	82	
3	M	4 days	2120	510	103	61	42	170	Breast milk
		At birth	2510	300	64	38	26	110	
8	M	10 days	2740	680	139	88	51	160	Breast milk +
		At birth	2570	270	64	44	20	103	citridol milk
2	F	4 days	2380	460	120	83	37	166	Breast milk
		At birth	2580	100	85	59	26	130	
9	M	4 days	2450	700	150	92	58	202	Breast milk
		24 days	3220	720	153	95	58	214	
39	F	At birth	2900	410	64	38	26	148	Breast milk
		3 days	2760	760	121	73	48	200	
40	F	At birth	2930	250	48	31	17	108	—
		5 hours		350	52	31	21	120	
10	F	At birth	2970	290	51	34	17	126	—
		1 hour		350	58	41	17	126	
42	F	At birth	3010	110	86	59	27	156	Citridol milk
		4 days	2800	560	131	86	45	194	
37	F	At birth	3030	230	69	41	28	128	Breast milk
		12 hours		300	71	41	30	140	
11	F	36 hours		570	110	69	41	190	
		At birth	3070	210	50	29	21	88	Breast milk +
		2 hours		230	48	25	23	100	citridol milk
		18 hours		280	61	39	22	122	
		At birth	310	87	49	38	152	Breast milk	
		4 days	2940	750	167	119	48	242	

Case No.	Sex	Age	Weight	Total lipids	Total cholesterol	Ester. cholesterol	Free cholesterol	Phospholipids	Remarks
12	M	At birth	3220	360	77	.48	.29	170	Breast milk
		4 days	3100	530	152	109	.43	250	
4	F	At birth	3220	270	73	.51	.22	108	Breast milk
		4 hours		300	82	.56	.26	120	
		4 days		3000	590	130	.85	180	
35	M	At birth	3370	200	.45	.26	.19	80	Breast milk + citridol milk
		5 hours		230	.48	.27	.21	90	
		21 hours		290	.78	.48	.30	150	
13	M	At birth	3380	350	.98	.67	.31	152	Breast milk
		4 days	3100	670	160	112	.48	216	
15	F	At birth	3400	340	.72	.48	.21	116	Breast milk
		6 days	3200	760	141	.85	.59	260	
6	F	At birth	3440	200	.70	.46	.24	116	Breast milk
		4 days	3240	.420	110	.58	.52	234	
44	M	At birth	3440	230	.55	.33	.22	96	Breast milk
		12 hours		260	.57	.36	.21	112	
		38 hours		510	.86	.51	.35	200	
46	F	At birth	3500	240	.52	.33	.19	92	—
		11 hours		260	.62	.38	.24	100	
43	F	At birth	3530	250	.66	.43	.23	152	Breast milk
		10 hours		260	.73	.50	.23	160	
		36 hours		.410	104	.55	.49	230	
14	F	At birth	3640	320	.85	.51	.34	116	Breast milk
		4 days	3350	620	149	.97	.52	214	
15	F	At birth	3710	250	.60	.38	.22	120	Breast milk
		5 hours		290	.66	.42	.24	130	
		36 hours		360	—	—	37	166	
11	F	At birth	3760	—	—	—	—	—	112
		1.5 hours		250	.67	.59	.47	17	
		3		—	—	—	—	—	112

Table 3. *Serum lipoproteins in newborn fullterm infants during the first days after birth*

Case No.	Sex	Age	Weight	Total lipids	α -fraction	β -fraction	Start fraction	Remarks
5	M	At birth	2500	210	86	69	55	
		8 hours		250	97	88	65	
3	M	1 day	2120	540	108	275	157	
		At birth	2510	300	138	99	63	
8	M	10 days	2740	680	221	320	136	
		At birth	2570	270	111	92	67	
2	F	1 day	2380	460	147	202	111	
		At birth	2580	400	176	120	104	
9	M	1 day	2150	700	215	308	147	
		2½ days	3220	720	259	324	137	
10	F	At birth	2900	410	172	144	94	
		3 days	2760	760	266	327	167	
12	F	At birth	3010	440	176	158	106	
		1 day	2800	560	179	263	118	
37	F	At birth	3030	230	108	64	58	
		12 hours	3000	117	93	90		
11	F	36 hours		570	154	257	159	
		At birth	3070	210	86	63	61	
12	M	2 hours		230	90	78	62	
		18 hours		280	84	114	82	
		At birth	3070	310	121	115	74	
		4 days		750	225	352	173	
		At birth	3220	360	151	119	90	
		1 day	3100	530	180	238	142	

		F	At birth	3220	270	108	86	76
			4 hours		300	117	105	78
			4 days	3000	590	165	283	112
	35	M	At birth	3370	200	106	50	44
			5 hours		230	106	71	53
			21 hours		290	93	122	75
	13	M	At birth	3380	350	150	102	98
			4 days	3100	670	214	308	118
	15	F	At birth	3100	310	150	116	74
			6 days	3200	760	266	304	190
	6	F	At birth	3110	200	81	68	48
			4 days	3210	420	109	227	84
	44	M	At birth	3140	230	90	69	71
			12 hours		260	99	83	78
			38 hours		540	167	216	157
	46	F	At birth	3500	240	113	70	57
			8 hours		260	127	81	52
	43	F	At birth	3530	250	100	75	75
			10 hours		260	101	78	81
			36 hours		440	114	216	110
	44	F	At birth	3640	320	144	96	80
			4 days	3350	620	229	248	143
	45	F	At birth	3710	250	140	60	50
			5 hours		290	154	70	66
			36 hours		360	148	133	79
	44	F	At birth	3760	220	81	70	66
			13 hours		250	93	82	75
			31 hours		167	196	127	

Case No.	Sex	Age	Weight	Total lipids	z-fraction	z-fraction	Start fraction	Remarks
34	M	At birth	3810	180	88	52	.40	
		1 hours		210	92	63	.55	
		20 hours		300	102	120	.78	
		At birth	3900	170	71	51	.48	
7	F	3 days	3660	130	116	215	.99	
		At birth	4050	350	168	108	.74	
		4 days	3740	650	234	292	.124	
		At birth	4110	300	120	99	.81	
1	M	5 hours		330	132	106	.92	
		At birth	4170	220	101	70	.49	
		1 hours		260	114	83	.63	
		19 hours		340	136	122	.82	
38	M	At birth	4310	220	110	64	.46	
		8 hours		260	104	91	.62	
		24 hours		390	120	164	.106	
		At birth	5100	290	145	73	.72	
33	M	12 hours		310	170	92	.78	
		27 hours		370	177	100	.93	
		At birth	3650	220	106	64	.50	Sectio Caesarea
		4 days	3100	150	171	180	.99	
16	F	At birth	3310	300	135	90	.75	Sectio Caesarea
		4 days	3290	600	222	210	.138	
		Mean value in cord blood		276 ± 12	121 ± 5.6	86 ± 5.0	.68 ± 3.3	
		Range in cord blood		170—176	71—176	50—158	.10—106	

CHAPTER V

SERUM LIPIDS AND LIPOPROTEINS IN INFANTS AFTER THE FIRST FEW DAYS OF LIFE

It is apparent from the survey of literature and Table 1 that our knowledge of the serum lipids and lipoproteins in normal infants is still incomplete. As a rule, only the total cholesterol has been studied and in only three publications have the phospholipids also been made the subject of investigation. The series on record are as a rule small. GYÖRGY (1926) found a slight increase of the total cholesterol and the phospholipids during the first year of life. MANICATIDE et al. (1927) and BAYLAC & SENDRAIL (1928) found low total cholesterol values throughout the first year of life. Recent investigations have found higher values for the total cholesterol in infants (HANSEN, 1937, RADWIN et al., 1940, and HODGE, SPERRY & ANDERSEN, 1943).

In order to form an opinion whether the serum lipids increase successively throughout the first year of life, it would be of interest to determine the serum lipids as well as the lipoproteins in the same infant at various intervals during this period. A search in the literature failed to reveal such an investigation.

MATERIAL

The present material consisted of infants admitted to the Childrens Hospital, Lund, or the Infants Home, Lund, on social grounds. As their stay there was not for the whole first year none of the infants were examined regularly throughout the entire first year of life. During the first five months of life 8 infants received breast milk (15 specimens) in a few cases with a little addition of citrido milk, 4 infants received only citrido milk (9 specimens) and 14 in-

fants (23 specimens) got cow's milk formula (50 per cent milk until 3 month of age and then about 70 per cent).

This group consisted of 37 infants, from whom 90 specimens were collected for analysis. In 13 of the infants one specimen was analysed. 12 infants were studied on two occasions, 6 on three, 7 on four and 2 on five occasions during the first year of life. The interval between two consecutive determinations varied from about one to about three months. All 90 analyses comprised the determination of total lipids, total and free cholesterol and phospholipids and in 70 analyses also of the lipoproteins.

RESULTS

The results of the individual analyses are given in Tables 4 and 5. The tables include an "initial" determination and sometimes "subsequent" determinations in each infant. Below the infants are classified according to age at the time of the "initial" determination and the "subsequent" determinations.

Age	Number of	
	initial determinations	subsequent determinations
3-10 days	4	—
11-30 "	4	—
2 months	5	5
3 "	5	4
4 "	6	3
5 "	2	6
6 "	1	8
7 "	2	3
8 "	3	3
9 "	1	6
10 "	2	4
11 "	1	5
12 "	1	5
13 "	—	1
Total	37	53

If we disregard the fact that several observations were made in one and the same infant and treat all the observations as if each were made in a separate infant, it will give the following results:

Mg 100 ml	Number of observ.	Mean value	Range
Total lipids	90	606	240—800
Total cholesterol	89	130	69—173
Free cholesterol	89	40	27—66
Combined cholesterol	89	90	51—132
Phospholipids	90	188	122—276
α -lipoproteins	70	169	67—281
β -lipoproteins	70	290	122—450
Start-fraction	70	124	51—247

The mean error is not calculated because the observations are not independent of one another. Tables 4 and 5 distinctly show appreciable fluctuations in lipid values during the first year of life. If we calculate the standard deviation of all the observations, it will be found to be 112 units (mg per 100 ml) for the total lipids, 23.7 units for the total cholesterol and 28 units for the phospholipids. It is obvious from a glance at Tables 4 and 5 that also the values in the same infant differ from one occasion to another. The standard deviation of the individual cases (in infants for whom two or more determinations were made) is not so great as that of the total number of observations.¹ For total lipids it was 81 units, for total cholesterol 18.8 units and for phospholipids 22.6 units.

In order to form an opinion as to whether any changes occur in the serum lipids during the first year of life, the data were first treated as if all the observations were entirely independent of one another. The observations classed according to the month of life are given below.

It is also possible to compare successive observations in one and the same infant and state how much the value has increased, whether it has persisted unchanged or whether it has decreased. It is also

¹ The standard deviation of the individual cases was derived by the formula:

$$S.D. = \sqrt{\frac{\sum_i \sum_j (x_{ij} - m_i)^2}{N - n}}$$

In this formula i denotes a given infant, x_{ij} the successive determinations of the same infant, i , and m the mean value for the infant, i . N denotes all the determinations and n the number of infants.

Month of life	Total lipids		Total cholesterol		Phospholipids	
	Number of cases	Mean mg 100 ml	Number of cases	Mean mg 100 ml	Number of cases	Mean mg 100 ml
1	8	580	8	133	8	194
2	10	605	10	120	10	189
3	9	608	9	132	9	194
4	9	561	9	123	9	163
5	8	619	7	121	8	176
6	9	558	9	116	9	174
7	5	596	5	131	5	172
8	6	670	6	139	6	235
9	7	581	7	132	7	179
10	6	618	6	131	6	198
11	6	658	6	149	6	200
12	6	647	6	153	6	206
13	1	540	1	149	1	156
1—3	27	599	27	128	27	192
4—6	26	578	26	120	26	171
7—9	18	615	18	134	18	195
10—13	19	615	19	145	19	199

possible to give the average total increase or the average increase per month. Average increase per month is to be understood here as the total increase divided by the total interval, between the successive observations. Analyses carried out in this way gave the following results:

Number of observations	Total lipids	Total cholesterol	Phospholipids
	Mg 100 ml	Mg 100 ml	Mg 100 ml
Increased	53	52	53
Unchanged	30	33	33
Decreased	2	0	2
Average increase	21	19	18
Average increase per month	38	8.5	7.2
	26	5.2	4.8

It is clear from the compilation that an increase between two successive observations was more common than a decrease. The statistical analysis of the subsequent determinations did not show

any definite increase, but neither did it exclude the occurrence of such an increase.²

It was also considered of interest to determine whether the ratio between combined cholesterol and free cholesterol was changed during the first year of life. As pointed out earlier (page 30), this ratio was much smaller for umbilical cord blood than for normal adults. During the first few days of life there appears to be no increase in the ratio between combined and free cholesterol.

Classification of the observations according to age of the infants gave the following compilation. For purpose of comparison, values for children 2—14 years old are included.

Age	Combined cholesterol		Free cholesterol	
	mg/100 ml	In per cent of total cholesterol	mg/100 ml	In per cent of total cholesterol
1—3 months	86	67	42	33
4—6 "	84	70	36	30
7—9 "	94	70	40	30
10—13 "	102	71	43	29
2—14 years	134	71	54	29

It is thus apparent that the combined cholesterol gradually increases in quantity, while the free cholesterol remains about the same. This implies that the ratio of combined to free cholesterol increases from about 2.0 during the first 3 months of life to about 2.5 at 10 to 13 months. The latter value corresponds to the value found for the older children, 2—14 years of age.

The various lipoprotein fractions found in the infants classed

² The mean error of the average increase on page 48 was derived by the formula:

$$\varepsilon = S.D. \sqrt{\frac{2}{n}}$$

Here *S.D.* denotes the value calculated by the formula in footnote 1, and *n* denotes the number of infants, on whom two or several determinations were made (27 infants). The mean errors are about 30 per cent of the standard deviations. The differences are thus somewhat greater than the mean errors but only in one case somewhat greater than 1.5 times the mean error.

according to age are given below. For purpose of comparison, values for children 2—14 years old are included in the compilation.

Age	Means of			Start fraction		
	α -lipoproteins		β -lipoproteins			
	mg 100 ml	In per cent of total lipids	mg/100 ml	In per cent of total lipids	mg 100 ml	In per cent of total lip.
1—3 months	157	30	243	46	125	24
4—6 "	168	31	273	50	104	19
7—9 "	163	27	312	51	131	22
10—13 "	183	29	322	50	140	21
2—14 years	251	30	412	49	176	21

It is apparent that although the ratio in the various age classes is approximately the same, all fractions show a tendency to increase with age.

It was also considered of interest to form an opinion of the individual variations in the cholesterol fractions and the lipoprotein fractions. The data obtained from the initial determination from each infant were therefore studied. The purpose of this analysis was to determine whether the ratio of combined to free cholesterol varies with the total cholesterol level and whether the distribution of the lipoprotein fractions varies with the total lipid level. The infants were grouped according to cholesterol value and total lipid value into three groups and the means of the components were determined as well as the ratio between them. The results are summarised below.

Total cholesterol mg 100 ml	Number of infants	Total cholesterol	Means in mg 100 ml of			Percentage of combined cholesterol
			Combined cholesterol	Free cholesterol		
—99	9	92	59	33		65
100—139	16	124	85	39		69
140—	12	153	107	45		70

Total lipids mg 100 ml	Number of infants	Total lipids mg 100 ml	α -lipoprot. mg 100 ml	β -lipoproteins			Start fraction mg 100 ml
				%	mg 100 ml	%	
—490	9	411	124	30	191	46	97 24
500—590	10	552	157	29	276	49	119 22
600—	18	671	171	26	352	52	148 22

It is apparent from the above figures that all the components contributed to the increase, but that the proportion of free cholesterol in sera containing a larger quantity of total cholesterol was smaller than when the total cholesterol of the sera was low, i. e. the ratio between combined and free cholesterol increase with the total cholesterol.

An increasing amount of total lipids was associated with a relative decrease in the α -lipoproteins, while the β -lipoproteins showed a relative increase. However, all the components showed an absolute increase.

Generally speaking, then, these differences were of the same type as those seen with increasing age of the infant.

COMMENTS

As is apparent from the survey of literature and from Table 1, the total serum cholesterol ranges between 100 and 200 mg/100 ml during the first year of life. While most authors used older methods of analysis, HODGE, SPERRY & ANDERSEN used the method described by SCHOENHEIMER & SPERRY (1934) and found the mean value for infants from the second month of life to be about 200 mg/100 ml. That method was used also in the present investigation and the mean cholesterol values found during the first year of life were much lower than those given by HODGE et al. This discrepancy calls for a few remarks. As mentioned earlier, SPERRY (1936) found the mean value for cholesterol during the first month of life to be 133 mg/100 ml. The results are founded on an objective investigation of sera from healthy infants. HODGE et al., on the other hand, selected their normal infants (43 cases) from a large hospital material (1934 to 1942). The other infants with diseases known or suspected to disturb the cholesterol metabolism were excluded. HODGE et al. thus found that infants that lost in weight had a mean cholesterol value of 123 mg/100 ml, that infants with uncomplicated anemia had a mean value of 126 mg/100 ml and children with infection and loss of body weight had a mean value of 116 mg/100 ml. Neither SPERRY (1936) nor HODGE et al. (1943) demonstrated

a marked increase in total cholesterol between the first and second month of life. Neither was such an increase found in the present investigation. By successive investigations on the same infants at varying intervals it was found in the present investigation that the values fluctuated widely during the first year of life with a slight tendency to increase towards the end of this period. This tendency applies not only to the total cholesterol, but also to the total lipids and phospholipids. The variation in the level of the serum lipids in infants has apparently not been made the subject of investigation before. WAMBERG (1953) determined the total lipids, phospholipids and cholesterol fractions in sera from 8 children aged 1—3 years at intervals of a few days or weeks and found fluctuations of about the same order as that noted in the present investigation.

Even in adults SPERRY (1937) found individual fluctuations for total cholesterol of about the same order as that recorded in infants in the present investigation. PETERS & MAN (1943) found for total cholesterol and phospholipids the spread of the serial individual values to be smaller than for the group as a whole.

According to SPERRY, the ratio between combined and free cholesterol "is one of the constants of the human body, and as far as I know, the only one to have been established with certainty among lipids". It is of interest to note that this ratio is much lower at birth and during the first months of life than for adults. At the end of the first year the ratio seems to approach that for normal adults.

The ratio between cholesterol and phospholipids is lower during the first year of life than in adult age. This has been pointed out also by GYÖRGY, who claims that this ratio has "eine besondere Bedeutung für die Zellpermeabilität, Giftwirkung, dann aber auch für Zellatmung und Erregbarkeit, ja für fast sämtliche Zellfunktionen überhaupt". AHRENS & KUNKEL (1949) claim that "the concentration of serum phospholipids available for complex formation with serum proteins appears to be an important factor in determining particle size of serum lipids and hence of their occurrence in serum as masked or as visible particles".

SUMMARY

The successive analysis of specimens from the same infants during the first year of life showed that the values for serum lipids and lipoproteins vary widely. The spread of serial individual values was, however, not so great as for the group of infants as a whole.

The serum lipids and lipoproteins showed a tendency to increase towards the end of the first year.

The ratio between combined and free cholesterol also showed an increase towards the end of the first year.

The ratio between cholesterol and phospholipids was found to be lower for infants than for adults.

Analysis of individual variations in cholesterol fractions showed the ratio of combined to free cholesterol to increase with total cholesterol. With increasing total lipids the proportion of α -lipoproteins decreased and that of β -lipoproteins increased. However, all the lipoprotein components showed an absolute increase.

Table 4. Serum lipids in infants during the first year

Case No.	Sex	Age	Birth weight	Weight	Total lipids	Total chol.	Ester. chol.	Free chol.	Phospholipids	Remarks
66	F	9 days	2530	2540	600	108	68	40	232	Breast milk
		32 "		3350	660	110	69	41	194	
		47 "		3850	600	141	99	42	194	
53	M	8 "	2520	2390	520	152	109	43	200	Breast milk
		10 "		3860	740	121	71	50	218	
72	M	3 "	2540	2280	610	130	80	50	174	Breast milk
		36 "		3020	610	124	84	40	180	
91	F	6 "	4220	3820	580	112	72	40	180	Cow's milk formula
92	F	11 "	3560	3400	530	99	71	28	158	Cow's milk formula
		52 "		3850	520	87	61	26	122	
97	"			5350	520	84	56	28	140	
		6 months		7550	550	98	71	27	158	
		12 "		—	610	134	97	37	170	
93	F	11 days	3450	3500	660	173	107	66	240	Breast milk + citrido milk
94	F	16 "	2990	3430	510	128	88	40	192	Breast milk
95	F	22 "	4360	5020	600	161	116	45	172	Citrido milk
		67 "		5910	730	144	101	43	174	
96	M	51 "	2700	4100	380	116	85	31	164	Cow's milk formula
		92 "		4900	660	157	115	42	224	
97	F	34 "	4510	5050	640	97	60	37	206	Breast milk
98	F	44 "	4180	4980	510	120	80	40	189	Breast milk
99	M	45 "	4700	5860	616	155	107	48	204	Citrido milk
		80 "		7020	760	115	105	40	216	
100	F	75 "	3130	4900	510	115	99	16	230	Cow's milk formula
101	F	76 "	2950	3550	550	115	99	16	230	

Citrido milk

99	M	45	"	1700	5860	616	155	107	.48	20 i
		80	"		7020	760	145	105	10	216
100	F	75	"	3130	1900	540	145	99	16	230
101	F	75	"	2960	5540	330	97	60	37	Cow's milk formula
		5 months		6900	450	108	69	39	176	Cow's milk formula
102	M	60 days		3060	4480	750	128	84	44	Breast milk
		90 "		5550	780	152	95	57	250	
103	F	90	"	3100	4720	240	69	39	30	Cow's milk formula
104	F	90	"	2600	5150	590	126	81	45	Cow's milk formula
		5 months		5850	570	121	84	37	182	
		6 "		6330	600	138	95	43	194	
105	M	68 days		3810	5380	800	153	108	45	Citrido milk
		86 "		5940	700	157	115	42	182	
		4 months		6440	660	167	124	43	200	
		5 "		7480	730	166	119	47	170	
106	F	4	"	3230	7780	750	145	108	37	Citrido milk
		6 "		7750	610	105	75	30	170	
		7 "		8240	650	124	82	42	170	
		8 "		8720	800	170	116	54	218	
107	M	4	"	2500	5100	470	91	61	30	Cow's milk formula
		5 "		5750	710	121	81	40	196	
		6 "		7000	650	119	80	39	194	
		9 "		8100	660	113	75	38	172	
		10 "		8450	590	134	93	41	170	
108	F	4	"	2530	4630	460	93	65	28	Cow's milk formula
		5 "		5250	770	105	69	36	188	
		7 "		6140	770	126	91	35	190	

Case No.	Sex	Age	Birth weight	Weight	Total lipids	Ester. chol.	Free chol.	Phospho-lipids	Remarks
109	F	4 "	3190	5700	680	130	99	31	Cow's milk formula
		5 "		6450	570	106	75	31	152
110	F	4 "	3800	6800	110	99	59	10	Cow's milk formula
		6 "		7500	180	104	65	39	168
111	F	4 "	3270	5580	110	138	94	44	Cow's milk formula
		6 "		6470	180	124	85	39	192
112	M	5 "	4530	7950	630	121	88	33	Cow's milk formula
		6 "		8600	610	135	97	38	156
		8 "		9800	780	144	103	41	162
113	M	5 "	3000	6170	520	—	—	33	Cow's milk formula
		6 "		6900	510	126	87	39	170
		9 "		8000	660	113	84	29	160
		10 "		8700	600	142	103	39	192
114	F	6 "	3290	6590	530	95	69	26	Cow's milk formula
		7 "		6950	560	142	101	41	172
		9 "		7000	600	144	100	44	178
		11 "		7510	740	157	105	52	230
		12 "		7910	680	163	115	48	192
115	M	7 "	3360	7850	580	127	92	35	Cow's milk formula
		8 "		8500	590	134	101	33	150
		9 "		9200	610	129	85	44	176
		12 "		9550	680	152	108	44	232
116	F	7 "	3410	7750	490	135	97	38	Cow's milk formula
		9 "		8220	500	112	99	43	196
		12 "		8810	570	156	110	16	206
		13 "		9050	510	119	110	39	156

9	9		2110	770	+90	153	97	38	168	
			8220	500	142	99	43	196		
			8810	570	156	110	46	206		
			9050	510	119	110	39	156		
			9250	480	124	88	36	124		
			9300	460	102	69	33	154		
			9530	650	152	105	47	212		
			8600	730	173	132	41	220		
			8700	610	155	110	45	204		
			7750	640	88	51	37	190		
			7970	750	133	95	38	202		
			8600	730	173	126	47	228		
			9630	570	130	96	44	164		
			10780	470	119	80	39	178		
			11290	650	150	104	46	200		
			3890	570	133	—	—	196		
			11	“	8200	730	48	102	46	
			12	“	3100	740	141	97	44	
			10	“	2800	8810	146	109	37	
			10	“	3000	7800	—	—	—	
			11	“	8200	730	48	102	46	
			10	“	3100	740	141	97	44	
			11	“	2800	8810	146	109	37	
			12	“	2820	10660	570	123	85	
			M	12	“	—	—	—	176	

Table 5. Serum lipoproteins in infants during the first year

Case No.	Sex	Age	Birth weight	Weight	Total lipids	β -fraction	α -fraction	Start-fraction
66	F	9 days	2530	2540	600	162	276	162
		32 "		3350	600	185	264	211
		47 "		3850	600	210	264	126
53	M	8	2520	2390	520	177	234	109
		10 "		3860	740	207	370	163
91	F	6 "	4220	3820	580	197	278	105
92	F	11 "		3400	530	148	265	117
		52 "		3850	520	156	239	125
		97 "		5350	520	182	234	104
		6 months		7550	550	171	217	132
		12 "		—	610	165	305	110
96	M	51 days	2700	1100	380	99	182	99
		92 "		4900	660	185	337	138
100	F	75 "		3130	4900	540	151	248
101	F	75 "	2960	5310	350	112	139	79
		5 months		6900	450	157	203	90
103	F	90 days	3100	1720	240	67	122	51
104	F	90 "	2600	5150	590	165	283	142
		5 months		5850	570	148	296	126
		6 "		6330	600	180	300	120
107	M	4 "	2500	5100	470	179	188	103
		5 "		5750	710	241	311	128
		6 "		7000	650	176	344	150
		9 "		8100	660	218	284	158
		10 "		8150	207	—	218	135

6	6	7000	710	241	544	128
			650	176	344	150
9	9	8100	660	218	284	158
10	10	8150	590	207	218	135
108	F	2530	4630	460	166	189
			5250	770	262	370
			6110	770	208	400
109	F	3190	5700	680	204	340
			6150	570	200	257
110	F	3800	6800	440	114	194
			7500	480	144	240
111	F	4270	5580	410	123	189
			6170	480	144	240
112	M	54530	7930	630	176	315
			8600	610	165	311
			9800	780	281	359
			10500	760	266	342
113	M	53000	6170	520	135	281
			6900	510	102	306
			8000	460	110	253
			8700	600	192	264
114	F	63290	6590	530	143	276
			6930	560	112	280
			7000	600	180	264
			7510	740	178	407
			7910	680	231	320
115	M	73360	7850	580	151	336
						93

Case No.	Sex	Age	Birth weight	Weight	Total lipids	α -fraction	β -fraction	Start-fraction
		8 "	8500	590	148	330	112	
		9 "	9200	640	160	346	134	
		12 "	9550	680	204	340	136	
116	F	7 "	7750	490	132	210	118	
		9 "	8220	500	120	245	135	
		12 "	8840	570	165	285	120	
		13 "	9050	540	178	259	103	
117	M	8 "	9250	480	120	274	86	
		10 "	9300	460	143	216	101	
		11 "	9530	650	156	351	143	
118	F	8 "	8600	730	168	380	182	
		9 "	8700	640	173	327	140	
119	M	8 "	7750	640	166	372	102	
		10 "	7970	750	180	450	120	
		12 "	8600	730	204	387	139	
120	F	9 "	9650	570	165	285	120	
		11 "	10780	470	122	240	108	
		12 "	11290	650	175	305	170	
121	F	10 "	3000	7800	750	195	360	195
		11 "	8200	730	241	307	182	
122	F	10 "	3100	7480	740	155	437	148
123	F	11 "	2800	8810	600	144	336	120
124	M	12 "	1820	10660	570	142	274	154

CHAPTER VI

SERUM LIPIDS AND LIPOPROTEINS IN 2-14 YEAR OLD CHILDREN

Using modern methods of analysis THOMAS (1947), KORNERUP (1948) and WAMBERG (1954) found the serum lipid level to be of about the same order as for adults. They could find no relation between age and serum lipid levels. Nor did HODGE, SPERRY & ANDERSEN find any increase in total cholesterol with increasing age.

A search of the literature failed to reveal any investigations of the serum lipids and lipoproteins in one and the same series of children. The purpose of this investigation, which was carried out on 2-14 year old children, was to form an opinion of the way in which such children differ from infants (below 1 year) in serum lipid and lipoprotein levels. The material consisted of 25 children who had been referred to the children's hospital because of mental disorders or some kind of examination. A few of the subjects were healthy children from outside the hospital.

RESULTS

Tables 6 and 7 give the results of the determinations in the individual cases.

The following data were obtained for the material as a whole, without respect to sex or age.

Mg/100 ml	Mean value	Range
Total lipids	838±32	490—1090
Total cholesterol	188± 5.0	138— 242
Combined cholesterol	134± 3.7	99— 173
Free cholesterol	54± 1.7	39— 69
Phospholipids	235± 5.3	188— 292
α -lipoproteins	251± 9.7	147— 327
β -lipoproteins	412±16	225— 541
Start-fraction	176± 9.0	98— 268

As shown on page 47, the infants differed from the older children both with regard to the mean values and the highest values. The differences cannot be ascribed to the smallness of the material or to chance. Statistical analysis revealed that the difference between the group of older children and the group of infants was highly significant for all the serum lipids and lipoproteins.¹

The ratio of combined to free cholesterol for the older children was 2.5 on the average. The same ratio for the total group of infants was 2.3.

Also the ratio of total cholesterol to phospholipids was on the average higher for the older children than for the infants, namely 0.80 as against 0.70.

COMMENTS

In the present investigation the total cholesterol value agreed with that of WAMBERG, while THOMAS and KORNERUP found somewhat higher values. THOMAS obtained lower values for total lipids than KORNERUP, WAMBERG and the present investigator. The phospholipid value found in the present investigation was somewhat higher than in the three investigations mentioned above. KORNERUP and WAMBERG used the methods of BRUN for the investigation of total lipids as well as of phospholipids. POSBORG PETERSEN, who used the same method of analysis as the writer for the determination of the phospholipids, found an average value of 220 mg/100 ml for normal adults. The observation that the phospholipids were higher for older infants than for adults agrees with the finding of KORNE-

¹ As not all of the observations for the infants (below 1 year of age) were independent of one another, the mean error was not calculated. It might, however, be mentioned that the standard deviation of the total lipid values in the infants was 112 units (mg per 100 ml). The material consisted of 90 observations in 37 infants. With complete agreement between the observations in the same infants the mean error would be of the order of 25 units. If the observations made in the same infant are regarded as independent of one another, the mean error would be 12 units. At any rate the difference between the older group of children and the infants ($838 - 606 = 232$ mg per 100 ml) is highly significant. This also holds for the other serum lipids and lipoproteins.

RUP, who reported a statistically higher mean value for children than for adults.

As mentioned in the preceding chapter, all the serum lipids studied during the first year of life showed wide individual fluctuations with a slight tendency to increase towards the end of the first year. The results obtained in the older children suggested that during the second year of life the serum lipid level gradually increased until it reached levels found in older children. The increase of the ratio between combined and free cholesterol and the ratio between total cholesterol and phospholipids from infancy also showed that in older children there is an adaptation of serum lipid and lipoprotein values toward adult levels.

Table 6. *Serum lipids in children from 2 to 14 years of age*

Case No.	Sex	Age	Total lipids	Ester chol.	Free chol.	Phospho- lipids	Remarks
125	M	1.5 years	980	129	60	250	D. Observatio
126	M	2 "	660	118	48	198	—
127	M	2 "	990	171	54	220	D. Observatio
128	F	3 "	950	226	65	242	—
129	F	4 "	670	207	149	58	D. Bronchitis ac. san.
130	F	4 "	690	193	125	68	D. Encephal. ac.
131	F	5 "	880	204	146	58	—
132	M	5 "	1030	193	134	59	D. Nephrit. ac. sanat.
133	F	6 "	940	166	120	46	D. Epilepsia?
134	F	7 "	1080	242	173	69	—
135	M	7 "	610	189	136	53	D. Enuresis nocturna
136	M	7 "	830	195	140	55	D. Enuresis nocturna
137	F	8 "	1090	204	146	58	D. Observatio
138	M	8 "	790	153	113	40	D. Commissio cerebri
139	F	9 "	490	138	99	39	D. V.O.C. congen.
140	F	9 "	720	203	145	58	D. Observatio
141	M	9 "	1010	215	160	55	D. Stat. post. encephal.
142	M	9 "	970	203	152	51	D. Neurasthenia
143	M	9 "	890	198	142	56	D. Neurasthenia
144	M	12 "	760	212	149	63	D. Nephrit. ac. sanat.
145	M	12 "	700	144	105	39	D. Psychopathia
146	F	12 "	690	177	130	47	D. Febris rheum.
147	F	13 "	800	161	117	44	D. Encephalopathy posttraum.
148	F	14 "	920	170	120	50	—
149	F	14 "	780	184	132	52	D. Commissio cerebri?

Table 7. Serum lipoproteins in children from 2 to 14 years of age

Case No.	Sex	Age	Total lipids	α -fraction	β -fraction	Start fraction
125	M	1.5 years	980	294	451	235
126	M	2 "	660	191	284	185
127	M	2 "	990	327	445	218
128	F	3 "	950	266	465	219
129	F	4 "	670	181	355	134
130	F	4 "	690	262	317	111
131	F	5 "	880	282	422	176
132	M	5 "	1030	257	505	268
133	F	6 "	940	263	461	216
134	F	7 "	1080	324	540	216
135	M	7 "	610	183	329	98
136	M	7 "	830	249	423	158
137	F	8 "	1090	316	534	240
138	M	8 "	790	261	395	134
139	F	9 "	490	147	225	118
140	F	9 "	720	216	367	137
141	M	9 "	1040	302	541	197
142	M	9 "	970	272	485	213
143	M	9 "	890	240	454	196
144	M	12 "	760	243	372	145
145	M	12 "	700	217	343	140
146	F	12 "	690	193	366	131
147	F	13 "	800	232	424	144
148	F	14 "	920	276	460	184
149	F	14 "	780	273	328	179

CHAPTER VII

SERUM LIPIDS AND LIPOPROTEINS IN PREMATURE NEWBORNS

A search of the literature failed to reveal any investigation of serum lipids and lipoproteins in premature newborns. It was now thought of interest to find out whether premature newborns differ from fullterm newborns in serum lipids and lipoproteins at birth and the first few days of life.

MATERIAL

The material consisted of 19 premature infants. The weight at birth varied between 1350 and 2430 grams. The serum lipids and lipoproteins were determined both in the umbilical cord blood and 3—26 days later in the capillary blood. Owing to the prematurity of the infants, samples of capillary blood were usually collected later than from the fullterm infants. Of the infants, 7 were twins. The mothers had felt well during pregnancy and the premature delivery was not due to any known disease. In one case the fetus was in transverse position and extraction was necessary. All the other deliveries were uncomplicated. Physical examination of the infants revealed nothing of interest over and above their prematurity. During the first 1—2 days after delivery the infants received only breast milk. From then on they received an addition of 20—30 grams citrido milk daily.

RESULTS

The results obtained in the individual cases are given in Tables 8 and 9. The mean values and variation ranges for serum lipids and lipoproteins are given below.

Mg 100 ml	At birth		3-26 days after birth	
	Mean value	Range	Mean value	Range
Total lipids	306±13	210—400	537±22	380—730
Total cholesterol	67± 3.5	47— 98	117± 6.6	83—167
Combined cholesterol	44± 2.5	28— 67	74± 5.5	43—119
Free cholesterol	23± 1.1	16— 31	45± 1.9	27— 62
Phospholipids	102± 6.4	40—142	191±10	126—260
α -lipoprotein	122± 5.3	78—160	156± 9.6	87—255
β -lipoprotein	98± 6.3	55—156	247±13	152—347
Start-fraction	86± 3.6	64—115	133± 5.7	96—198

On comparison with corresponding lipid values in serum from umbilical cord blood from 15 fullterm infants (see page 29) it was found that the range of variation for both series showed good agreement. The phospholipids showed, however, lower values for the premature infants. Statistical analysis showed that the spread of the lipid values was so great that no difference can be said to occur.

As is apparent from the compilation above, there was a marked increase of all the serum lipid values during the first days of life. This increase was not so large as for the fullterm infants in spite of the longer interval between birth and the collection of samples from the premature infants.

The increase found in the serum lipids after birth in premature and fullterm infants is apparent from the following figures:

Material	Mean time in days	Number	Mean increase (mg 100 ml) in		
			total lipids	total cholesterol	phospho- lipids
Fullterm	3.9	15	295	60.0	83.1
Premature	7.5	19	232	50.6	85.8

It is thus apparent that despite the longer interval between the determinations, the total lipids and the total cholesterol showed a smaller increase in the premature infants.

As to the ratio of combined and free cholesterol, it showed about the same range and mean value as for fullterm infants, both at birth and some days later. This also applies to the ratio between total cholesterol and phospholipids.

The changes in the distribution of the lipoprotein fractions were of the same order as for the fullterm infants. The α -lipoproteins

decreased from on the average 40 per cent to 29 per cent, while the β -lipoproteins increased from 32 per cent to 46 per cent.

Summing up, the increase in serum lipids during the first few days of life showed a tendency to be smaller in premature infants than in fullterm infants. No other differences were found between the premature and fullterm infants.

Table 8. Serum lipids in cord blood and capillary blood in premature infants

Case No.	Sex	Age	Weight	Total lipids	Total chol.	Ester chol.	Free chol.	Phospholipids	Remarks
62	M	At birth	1350	260	77	51	26	120	Twin
		26 days	1560	640	124	66	58	284	
65	F	At birth	1350	320	77	47	30	40	Twin
		8 days	1100	520	152	109	43	200	
67	F	10 "	2450	740	121	71	50	218	
		At birth	1620	300	79	59	20	116	Twin
68	F	9 days	1780	660	133	82	51	214	
		32 "	2410	620	121	89	32	208	
18	F	16 "	2920	500	113	74	39	176	
		At birth	1650	290	47	28	19	116	
19	M	6 days	1720	570	83	48	35	164	
		39 "	3060	700	124	79	45	204	
26	F	At birth	1660	260	49	32	17	71	
		10 days	1700	410	86	59	27	156	
19	M	46 "	2680	720	119	78	41	192	
		At birth	1660	270	48	30	18	72	
20	M	7 days	1700	390	103	68	35	126	
		30 "	2550	740	133	83	50	176	
20	M	At birth	1910	400	77	51	26	138	
		4 days	1750	500	88	48	40	180	
21	M	44 "	3420	570	144	94	50	192	

Case No.	Sex	Age	Weight	Total lipids	Total chol.	Free chol.	Phospho-lipids	Remarks
32	M	At birth	1950	400	49	29	20	100
		7 days	2250	730	97	59	38	170
54	F	At birth	2010	330	81	51	30	Twin
		6 days	2010	520	138	91	47	190
29	F	At birth	2040	320	56	33	23	108
		5 days	2100	600	145	83	62	260
		25 "	3010	610	149	87	62	206
28	M	At birth	2110	210	59	40	19	98
		16 days	2420	520	142	93	49	206
		30 "	3060	560	130	86	44	214
31	M	At birth	2120	400	71	47	24	129
		4 days	2000	580	99	55	44	164
		26 "	2900	530	128	81	47	220
		46 "	3750	610	135	90	45	176
27	F	At birth	2150	340	76	52	24	94
		6 days	2070	620	149	95	54	216
		29 "	3000	580	124	82	42	202
68	M	At birth	2160	300	48	32	16	98
		4 days	2100	510	126	74	52	164
		29 "	3160	510	131	83	48	160
59	M	At birth	2160	230	68	48	20	100
		5 days	1970	410	84	43	41	162
		24 "	2370	530	127	81	46	238
21	F	At birth	2200	350	98	67	34	142
		"	"	"	"	"	"	"

			At birth	2000	350	98	67	51	42
64	F		4 days	2000	610	160	116	44	228
		27 "	At birth	2700	700	145	95	50	244
		8 days	2210	300	80	54	26	60	Twin
		24 "	2060	510	167	119	48	242	
		54 "	2680	550	141	93	48	212	
		54 "	4260	580	144	98	46	236	
25	M		At birth	2310	280	75	52	23	82
		5 days	2170	380	88	47	41	148	
		28 "	3000	530	131	88	43	202	
58	M		At birth	2430	260	64	43	21	110
		3 days	2220	480	91	51	40	168	
		24 "	2650	550	135	88	47	250	

Table 9. Serum lipoproteins in cord blood and capillary blood in premature infants

Case No.	Sex	Age	Weight	Total lipids	α -fraction	β -fraction	Start fraction	Remarks
62	M	At birth	1350	260	122	73	65	Twin
		26 days	1560	640	186	301	153	
65	F	At birth	1350	320	144	96	80	Twin
		8 days	2390	520	177	234	109	
67	F	At birth	1620	300	207	470	163	Twin
		9 days	1780	660	117	96	87	
		32 "	2410	620	130	335	155	
18	F	At birth	1650	290	145	230	125	
		6 days	1720	570	182	239	139	
		39 "	3060	700	217	315	168	
26	F	At birth	1660	260	96	73	91	
		10 days	1700	440	132	202	106	
		46 "	2680	720	194	324	202	
19	M	At birth	1660	270	113	76	81	
		7 days	1700	380	99	152	129	
		30 "	2550	740	222	333	185	
20	M	At birth	1910	400	160	152	88	
		4 days	1750	500	165	225	110	
		14 "	3420	570	171	268	131	
32	M	At birth	1950	400	164	124	112	
		7 days	2250	730	255	329	146	
54	F	At birth	2040	330	139	92	99	
		6 days	2040	520	176	219	125	
29	F	At birth	2100	320	122	115	83	
		5 days	2100	600	150	288	162	
		25 "	3010	610	177	317	116	
		At birth	2110	210	90	55	65	

29	F		At birth	2040	320	122	115	83
		5 days		2100	600	150	288	162
28	M		25 "	3010	610	177	317	116
		At birth		2110	210	90	55	65
		16 days		2120	520	182	203	135
30	"		3060	560	179	241	140	
31	M		At birth	2120	400	140	156	104
		4 days		2000	580	157	307	116
		26 "		2900	530	138	260	132
		46 "		3750	610	189	256	165
27	F		At birth	2150	310	139	86	115
		6 days		2070	620	136	347	137
		29 "		3000	580	191	261	128
68	M		At birth	2160	300	120	81	96
		4 days		2100	510	143	224	143
59	M		29 "	3160	540	135	243	162
		At birth		2160	230	97	69	64
		5 days		1970	410	123	180	107
21	F		24 "	2370	530	170	228	132
		At birth		2200	350	151	98	101
		4 days		2000	610	183	281	146
		27 "		2700	700	196	392	112
64	F		At birth	2210	300	126	96	78
		8 days		2060	510	184	230	96
		24 "		2680	550	187	259	104
		54 "		4260	580	203	249	128
25	M		At birth	2310	280	78	137	65
		5 days		2170	380	87	179	114
58	M		28 "	3000	530	159	207	164
		At birth		2130	260	96	86	78
		3 days		2220	480	106	230	144
		24 "		2650	550	143	264	143

CHAPTER VIII

SERUM LIPIDS AND LIPOPROTEINS IN PREMATURE INFANTS DURING THE FIRST FEW MONTHS OF LIFE

As the premature infants were cared for at the children's hospital until they had reached a body weight of about 3000 grams, it was possible to make successive serum analyses. The material consisted of 37 premature infants (67 specimens). In none of these cases was prematurity attended by any complications during hospitalisation, and increase in body weight was normal throughout. Most of the children received mainly breast milk with an extra daily feed of 30—40 grams citrido milk. Some of the infants received mainly citrido milk.

RESULTS

Tables 8, 9, 10 and 11 give the results of the individual analyses. The first value after birth is called the "initial" determination and the values thereafter "subsequent" determinations. The determinations grouped according to age class are given below.

Age	Initial determination	Subsequent determinations
3—10 days	22	—
11—30 "	9	16
2 months	3	10
3 "	1	2
4 "	2	—
9 "	—	2

Since the serum lipid values for premature infants during the first few days of life had proved lower (page 67) than for fullterm infants, the values recorded for premature infants during the first 10 days of life were not included in the first statistical analysis.

If we disregard the fact that several observations were made in

the same infant and treat all the observations as if each referred to a separate infant, the analysis would give the following values for the premature infants and for the fullterm infants. It should be pointed out that the observations for the fullterm infants span the first year of life, while those for the premature infants cover only the first months of life with the exception of the two observations made at 9 months.

Mg/100 ml	Material	Number	Mean value	Range
Total lipids	Fullterm	90	606	240—800
	Premature	45	610	430—770
Total cholesterol	Fullterm	89	130	69—173
	Premature	45	131	98—160
Phospholipids	Fullterm	90	188	122—276
	Premature	45	205	160—284

It is apparent that the values found for the fullterm infants did not differ appreciably from those found for the premature infants.

As pointed out in Chapter VII, in premature infants the serum lipids did not show such a marked increase as in fullterm infants during the first few days of life. This was also found to be so in the total group of premature infants. The average values found in 22 specimens collected from premature infants 3—10 days old are given below.

Total lipids	535 mg/100 ml
Total cholesterol	114 mg/100 ml
Phospholipids	183 mg/100 ml

In an attempt to form an opinion of the changes occurring in the serum lipids during the first 10 days of life and later, a comparison was made between the values found before and after the tenth day in 19 of the infants from whom specimens had been collected also after the tenth day. The results of this comparison are given below.

Mg/100 ml	Number of cases with values			Average increase
	increased	unchanged	decreased	
Total lipids	17	0	2	104
Total cholesterol	15	0	4	20
Phospholipids	12	1	6	20

In 10 of the cases determinations were made on two successive occasions after the tenth day. The corresponding values found in these were as follows.

Mg/100 ml	Number of cases with values			Average increase
	increased	unchanged	decreased	
Total lipids	7	0	3	38
Total cholesterol	7	0	3	7
Phospholipids	5	0	5	0

The values found after the tenth day of life were higher than those found before. This increase was more pronounced for the total lipids, for which it was statistically significant. Later determinations showed no further increase in these premature infants. The increase of serum lipids found for the 19 premature infants after the third to tenth day of life was of the same order as the difference between the serum lipid values for premature infants the third to tenth day of life and for the fullterm infants during the first year of life. What is said about serum lipids also holds for α - and β -lipoproteins.

COMMENTS

A search of the literature failed to reveal any reports of the serum lipids and lipoproteins in premature infants. Therefore no material is available for comparison of the observations made in the present investigation. It was found that in fullterm infants the serum lipids and lipoproteins increased during the first week of life to reach levels at which they persisted, on the whole, for the first few months of life, although wide individual variations may occur. In the premature infants, however, the serum lipids and lipoproteins increased successively during the first 3—4 weeks of life before they reached corresponding levels. After the first month of life, no difference was demonstrable between the premature and fullterm infants.

A question that then presents itself is: Why do the serum lipids and lipoproteins in premature infants require a longer time to reach constant level? In studies using fat-free diet during the first 3 days of life it was shown (page 91) that the increase in the serum lipids is less marked than if the diet contains ordinary fat. This might

suggest that the dietary fat contributes to the increase in serum lipids during the first few days of life. DROESE (1952) and HAUSER (1953) have shown that the fat absorption in newborns is decreased during the first few days of life. For the premature infants, however, the fat absorption is decreased for a longer time, as a rule, during the first months of life. The premature infants have been shown to have a smaller secretion of lipase and bile than fullterm infants during the first time after birth (DROESE 1952), which may also explain the deficient absorption of fat and perhaps also the slower increase in serum lipids and lipoproteins during the first month of life in premature infants.

Table 10. *Serum lipids in capillary blood from premature infants*

Case No.	Sex	Age	Weight	Total lipids	Total cholesterol	Ester. cholesterol	Free cholesterol	Phospho-lipids
71	M	At birth	1620	—	—	—	—	—
		4 months	5450	570	135	91	44	192
		9 "	8940	540	113	77	36	176
81	F	At birth	1720	—	—	—	—	—
		25 days	1950	530	135	85	50	236
		38 "	2180	670	138	88	50	230
74	F	At birth	1720	—	—	—	—	—
		3 days	1740	470	84	46	38	190
		24 "	2280	610	116	78	38	176
83	M	At birth	1820	—	—	—	—	—
		6 days	1680	390	90	47	47	210
		37 "	3000	430	98	59	39	180
86	F	At birth	1850	—	—	—	—	—
		25 days	2620	610	135	83	52	216
		At birth	1920	—	—	—	—	—
70	M	4 months	540	131	86	45	232	—
		9 "	500	108	74	34	176	—
		At birth	2020	—	—	—	—	—
85	M	12 days	2060	570	116	72	44	194
		At birth	2020	—	—	—	—	—
		3½ days	—	180	131	—	11	101
88	M	At birth	2040	—	—	—	—	—
		10 days	3310	610	129	81	15	180

			At birth	2020	180	141	111	101
			3 days					
88	F		At birth	2040	—	—	—	—
			10 days	3340	610	129	81	15
90	M		At birth	2100	—	—	—	180
			63 days	2600	580	119	79	40
75	F		At birth	2110	—	—	—	200
			7 days	2240	670	124	83	41
			17 "	2540	770	133	76	200
			25 "	2980	720	160	103	57
76	M		At birth	2150	—	—	—	226
			3 days	2060	480	75	38	—
			18 "	2740	580	99	64	144
			41 "	3850	610	145	99	35
73	F		At birth	2200	—	—	—	170
			3 days	2020	580	98	55	46
			16 "	2280	670	145	97	200
80	M		At birth	2300	—	—	—	—
			50 days	4260	710	189	137	52
			At birth	2350	—	—	—	162
			20 days	3100	710	110	78	48
82	F		At birth	2370	—	—	—	160
			23 days	2900	670	130	89	—
			At birth	2400	—	—	—	212
79	M		21 days	2830	620	119	79	—
			At birth	2460	—	—	—	150
81	F		23 days	3140	690	146	96	—
						50	228	—

Table 11. Serum lipoproteins in capillary blood from premature infants

Case No.	Sex	Age	Weight	Total lipids	α -fraction	β -fraction	Start fraction
71	M	At birth	1620	—	—	—	—
		9 months	8940	540	162	270	108
74	F	At birth	1750	—	—	—	—
		3 days	1740	470	169	169	132
		24 "	2280	610	183	244	183
		46 "	3300	630	220	284	126
		72 "	4340	560	174	263	123
70	M	At birth	1920	—	—	—	—
		9 months	—	500	155	225	120
90	F	At birth	2100	—	—	—	—
		63 days	2600	580	139	325	116
75	M	At birth	2110	—	—	—	—
		7 days	2240	670	215	328	127
		17 "	2540	770	269	385	116
		25 "	2980	720	224	338	158
76	F	At birth	2150	—	—	—	—
		3 days	2060	480	134	192	154
		18 "	2740	580	128	232	220
		41 "	3850	610	140	348	122
89	M	At birth	2350	—	—	—	—
		20 days	3100	710	213	312	185

CHAPTER IX

SERUM LIPIDS AND LIPOPROTEINS IN TWINS DURING THE FIRST FEW DAYS AFTER BIRTH

Whether the serum lipid level in the fetus is related to that in the mother has been made the subject of many investigations. SLEMONS & STANDER (1923) found the total cholesterol in maternal serum to be much higher than in serum from the fetus. This was confirmed by PLASS & TOMKINS (1923), GYÖRGY (1926) and HELLMUTH (1926). HELLMUTH was unable to demonstrate any correlation between the cholesterol and phospholipid values in the mother and those in the fetus. Some mothers with remarkably high serum lipid values had fetuses with remarkably low serum lipid values and vice versa.

A question that has apparently not received attention before is whether any difference in serum lipids can be demonstrated between twins.

MATERIAL

The material consists of 7 pairs of twins, 3 of which were enzygotic and 4 dizygotic. Umbilical cord blood was collected and 3—9 days after delivery capillary blood was drawn from all the infants. Further samples were also collected from the premature twins nursed on the hospital during the first month of life. Delivery was uncomplicated in all cases except one (transverse position). All of the infants received breast milk and, as a rule, complementary citrido milk.

RESULTS

The results are summarised in Tables 12 and 13. It is apparent from the compilation below that the twins did not differ from full-term and premature infants regarding the serum lipid and lipopro-

tein levels in the umbilical cord blood. The increase in serum lipids during the first few days of life was about the same as that found for the premature infants, as is seen in the compilation below.

Lipid values in serum from twins

Mg 100 ml	In cord blood		In capillary blood 3-9 days after birth	
	Mean value	Range	Mean value	Range
Total lipids	276	220-330	504	400-666
Total cholesterol	70	48-91	120	84-167
Ester cholesterol	48	32-60	75	43-119
Free cholesterol	22	16-31	45	38-55
Phospholipids	107	40-144	203	140-250
α -lipoprotein	116	95-144	147	112-194
β -lipoprotein	84	57-97	233	180-330
Start-fraction	76	58-99	130	96-198

This might be explained by the fact that most of the twins were premature infants. The twins in each pair did not differ appreciably from one another with regard to the serum lipid values and lipoprotein values of the umbilical cord blood.

During the first few days of life the serum lipids increased in some pairs at about the same rate in both twins and in other pairs of twins at relatively different rates.

Statistical analyses were carried out to find answers to the following questions:

Do twins of a pair differ from one another with respect to the total lipids and total cholesterol at birth?

Do twins of a pair differ from one another with respect to the total lipids and total cholesterol some days after birth?

In an attempt to find an answer to these questions the difference between the values noted for the two twins of each pair was determined. The differences were squared and the squares were summed as in the calculation of the error of the methods. The sum was divided by 14 (twice the number of pairs of twins). If the twins did not differ in the respect under consideration, the square root of the quotient should be of the same order as the error of the method.

It is thus apparent that the difference between the values noted for the pairs of twins at birth was twice that of the error of the method. Some days later this difference was appreciably greater.

At birth	Sum of squares	Quotient	Square root of quotient	Error of the method
Total lipids	4700	336	18	8—9
Total cholesterol	339	24.2	4.9	2.5
A few days after birth				
Total lipids	26500	1893	44	
Total cholesterol	2284	163	12.8	

This was also the case with the phospholipid and lipoprotein fractions. Another factor that must be borne in mind is that at the birth of twins changes might occur in the serum lipids in the placental circulation between the two deliveries. Therefore the agreement found between the serum lipids and lipoproteins in the umbilical cord of twins seems to be good.

It was of interest to note that despite the fact that the twins in each pair differed considerably in weight at birth, the serum lipids were nevertheless approximately equal.

No difference was found between enzygotic and dizygotic twins.

COMMENTS

One might expect to find agreement between the level of the serum lipids in umbilical cord blood in enzygotic twins. This was also found to be so.

It was also found that dizygotic twins did not differ with regard to the serum lipid level of the umbilical cord blood.

That there is no variation between pair of twins in serum lipids may be explained by the fact that during intra-uterine life both twins are living under identical conditions and receive nutrition from one and the same source.

That the maternal serum lipids are not presented to the fetus by simple diffusion, but by active secretion, has been shown by POPJAK (1947). He gave potassium phosphate labelled with radioactive phosphorus, P^{32} , to pregnant rabbits and later extracted the phospholipids from the maternal blood, the placenta and the fetal blood. He then estimated the amounts of P^{32} in the three purified phospholipids and showed that there was more in the placental

Table 12. Serum lipids in twins during the first days after birth in umbilical cord blood and capillary blood

Case No.	Sex	Age	Weight	Total lipid	Total chol.	Ester chol.	Free chol.	Phospholipids	Remarks
54 Twin I	F	At birth	2010	330	81	51	30	144	Icter. neon.
		6 days	2040	520	138	91	47	190	
55 Twin II	F	At birth	2610	330	72	45	27	150	Dizygotic twins
		6 days	2560	570	162	107	55	250	
56 Twin II	M	At birth	2590	250	75	47	28	130	Dizygotic twins
		3 days	2480	400	121	66	55	244	
57 Twin I	M	At birth	2920	250	71	45	26	110	Dizygotic twins
		3 days	2910	430	117	69	48	250	
58 Twin I	M	At birth	2430	260	64	43	21	110	Enzygotic twins
		3 days	2220	480	91	51	40	168	
59 Twin II	M	2 <i>i</i> "	2650	550	135	88	47	250	Enzygotic twins
		At birth	2160	230	68	48	20	100	
60 Twin I	M	5 days	1970	410	84	43	41	162	Enzygotic twins
		2 <i>i</i> "	2650	530	127	81	46	238	
61 Twin II	M	At birth	2500	220	58	36	22	110	Dizygotic twins
		3 days	2320	550	93	55	38	186	
62 Twin II	F	At birth	2600	250	66	40	26	128	Enzygotic twins
		3 days	2380	460	96	57	39	194	
63 Twin II	F	At birth	2210	300	80	54	26	60	Enzygotic twins
		8 days	2060	510	167	119	48	242	
64 Twin II	"	2 <i>i</i> "	2680	550	141	93	48	212	Enzygotic twins
		5 <i>i</i> "	4260	580	144	98	46	236	
65 Twin I	F	At birth	1350	320	77	47	30	40	Enzygotic twins
		8 days	1400	520	152	109	53	200	
66 Twin II	"	10 "	2450	710	121	71	50	218	Enzygotic twins

8 days									
10	"								
1:00		520							
2:16:0		7:10							
66	Twin II	F	At birth	2530	270	91	60	31	100
			9 days	2540	600	108	68	40	232
			32 "	3350	660	110	69	41	194
			47 "	3850	600	141	99	42	194
67	Twin I	F	At birth	1620	300	79	59	20	116
			9 days	1780	660	133	82	51	214
			32 "	2410	620	121	89	32	208
			46 "	2920	500	113	74	39	176
68	Twin I	M	At birth	2160	300	48	32	16	98
			4 days	2100	510	126	74	52	161
			29 "	3160	540	131	83	48	160
69	Twin II	F	At birth	2950	260	51	32	19	108
			4 days	2720	430	98	53	45	140

Transverse
position and
extraction

Enzygotic twins

Table 13. Serum lipoproteins from twins during the first days after birth^b

Case No.	Sex	Age	Weight	Total lipids	α -fraction	β -fraction	Start fraction	Remarks
54 Twin I	F	At birth	20.40	330	139	92	99	Dizygotic twins
		6 days	20.40	520	176	219	125	
55 Twin II	F	At birth	26.10	330	139	92	99	Dizygotic twins
		6 days	25.60	570	194	250	126	
56 Twin II	M	At birth	25.90	250	112	80	58	Dizygotic twins
		3 days	24.80	400	112	192	96	
57 Twin I	M	At birth	29.20	250	108	70	72	Dizygotic twins
		3 days	29.10	430	120	206	104	
58 Twin I	M	At birth	21.30	260	96	86	78	Enzygotic twins
		3 days	22.20	480	106	230	114	
59 Twin II	M	At birth	21.60	230	97	69	64	Enzygotic twins
		5 days	19.70	410	123	180	107	
60 Twin I	M	At birth	25.00	220	95	57	68	Dizygotic twins
		3 days	23.20	550	154	237	159	
61 Twin II	M	At birth	26.00	250	110	75	65	Dizygotic twins
		3 days	23.80	460	120	207	133	
64 Twin II	F	At birth	22.10	300	126	96	78	Enzygotic twins
		8 days	20.60	510	184	230	96	
54	"		26.80	550	187	259	104	Enzygotic twins
	"		12.60	580	203	219	128	

		Twin I	F						
55		At birth	1350	320	144	96	80		
		8 days	1400	520	177	234	109		
		10 "	2450	740	207	370	163		
56		At birth	2530	270	103	97	70		
		9 days	2510	600	162	276	162		
		32 "	3350	660	185	264	211		
		47 "	3850	600	210	264	126		
57		At birth	1620	300	117	96	87		
		9 days	1780	660	132	330	198		
		32 "	2410	620	130	335	155		
		46 "	2920	500	145	230	125		
								Twin I	Enzygotic twins

fraction than in either of the two blood fractions. Further experiments (POPJAK, 1952) have shown that the fetal placenta, although it absorbed phospholipids from the maternal circulation, is seen to have been an effective barrier against the passage of unhydrolysed phospholipid molecules from the mother to the fetus. The experiment led to the definite conclusion that all the phospholipids in the fetus, placenta of fetal origin being excluded, are synthesised in the fetus and are not derived from the preformed maternal compounds. It has also been shown that the fatty acids and cholesterol are formed within the fetus and that only a small proportion may be derived from the mother.

The fact that the serum lipid level in the umbilical cord blood of twins was about the same for both of them, suggests that the maternal organism may have a central regulatory effect on the fat metabolism in the fetus.

The next few days after birth the serum lipids in twins of one and the same pair differ and then suggest the influence of individual factors.

CHAPTER X

INFLUENCE OF THE DIET ON THE INCREASE OF THE SERUM LIPIDS AND LIPOPROTEINS DURING THE FIRST FEW DAYS OF LIFE

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The cessation of placental transmission and the onset of alimentary function at birth are of interest in the discussion of the increase in serum lipids and lipoproteins during the first few days of life. The metabolic products earlier received from the mother must now be substituted by products synthesised by the infant itself. These changes in metabolism are reflected in the respiratory quotient (R.Q.). BENEDICT & TALBOT (1915) showed that during the first hours of life the R.Q. is about 0.9 for fullterm infants, but decreases to 0.80 at the end of the first day. It then decreases further to 0.73 on the third day, after which it increases to 0.80 on the fifth to sixth day, at which level it afterwards persists. This implies that in the newborn the stored glycogen is rapidly consumed and that the infant then burns mainly fat during the first three days of life. The decrease of R.Q. is closely related to the successive increase of serum lipids and lipoproteins during this period. Whether the increase of serum lipids is due to the mobilisation of the fat reserves of the infant or to the alimentary fat has not been investigated before. It was therefore considered of interest to form an opinion of the extent to which this increase is due to the dietary fat. This could be assessed by giving the infant a fat-free diet the first 3 or 4 days of life. It is, however, difficult to interpret the possible effect of dietary factors on infants during the first few days of life, i. e., during a profound adaptation process to extra-uterine life. Many factors not known or not properly understood can readily lead to misinterpretations of the findings.

DIET

- I. During the first 3 or 4 days of life the infants received milk, from which the fat had been removed by centrifugation. The fat-

poor milk (containing 0.3—0.4 per cent fat) was then given in the form of citrido milk.

Preparation of citrido milk: Citrido tablets containing 0.37 gm of citric acid per tablet were dissolved in warm water. To the skimmed milk was added 10 per cent sugar, after which the mixture was heated to boiling point and then rapidly cooled. The solution of citric acid corresponding to 1 tablet per dcl of milk was then added dropwise during vigorous stirring.

II. As skimmed milk contains 0.3—0.4 per cent fat, during the first 3 or 4 days some of the infants received an artificial diet consisting of carbohydrates in the form of sugar and proteins in the form of amino acids ("Aminosol"). Aminosol is an amino acid preparation consisting of all the amino acids of protein, and it is prepared by dialysis of an enzymatic casein hydrolysate. To a 10 per cent solution of sugar was added 5—6 per cent "Aminosol".

III. Some infants received only carbohydrate in the form of 20 per cent solution of maltose during the first 3—4 days of life.

MATERIAL

It was difficult to get suitable material for these studies. It was necessary to limit the investigation to newborns, who for some reason or other were not allowed to receive breast milk. Therefore, all of the infants except one were from unmarried mothers who had decided to let their babies be adopted immediately after delivery. In one case the infant was taken from the mother immediately after delivery because of maternal pulmonary tuberculosis. As it was not known until after delivery that the infants were to be adopted, umbilical cord blood was not collected. Instead the capillary blood was collected as soon as circumstances permitted after delivery before the infant received its first meal. In only 3 cases, however, was the fasting period more than 13 hours.

After a blood specimen had been taken before the infant had received any food, it was placed on a special diet for 3—4 days. During this time the infant received 5 meals per day, the portion given at each meal being increased from one day to the next during the experiment. As a rule the infant received 80—100 gm on the

first day, about 200 gm on the second and about 300 gm on the third. The amount of food consumed during this period varied with the appetite of the infant. The caloric intake during this time was not calculated, because even under normal conditions consumption of breast milk can vary widely during the first few days. At the end of the experimental period, i. e. before the infants were allowed to have ordinary food (citrido milk prepared on cow's milk containing 3 per cent fat), new samples of blood were taken. In some cases it was possible to receive a further blood sample after the infant had been receiving citrido milk for 3—4 days.

In the infants, who were brought up on fat-poor citrido milk, the lipoprotein patterns were not determined. In the other two series both the serum lipids and lipoproteins were determined.

RESULTS

The material thus consisted of three groups, one in which the infants received carbohydrates and amino acids (G1), one in which they received carbohydrates only (G2), and one in which they received fat-poor citrido milk (G3). The results of the individual analyses are given in Tables 14—18. Table 19 gives the mean values for the various serum lipids and lipoproteins before and after the infants had received the experimental diet. For purposes of comparison this table includes corresponding means for 15 normal full-term infants, who received an ordinary diet during the first days of life. It is apparent from the table that G2 differed distinctly from G1 and G3. This is clear from the average increase from the first to the second determination.

Group	Mean increase in mg/100 ml		
	total lipids	total cholesterol	phospholipids
G1 + G3	150	31	37
G1	128	24	36
G2	21	3	9
G3	166	36	38
Normal	296	60	83

Statistical analysis of the data showed no increase in the total lipids, total cholesterol or phospholipids during the experiment in

G2. It is also apparent from Table 17 that in a few infants the values even decreased during the experiment. As no statistical difference was found between G1 and G3, these groups were taken together as a single group.¹

As pointed out in an earlier chapter, the serum lipids in capillary blood before the first meal were found to be about 10—15 per cent higher than for umbilical cord blood. Even when this difference was taken into account, G1 and G3 showed a smaller increase in serum lipids during the first days of life than newborns brought up on a normal diet. In group G1 the changes occurring in the relative

¹ In the group G2 the following values of standard deviation and the mean error of the mean are found:

	S. D.	Mean error
Total lipids	36	13
Total cholesterol	7.8	2.8

Thus, no increase can be said to occur in this group.

For the other two groups, G1 and G3, the common standard deviation was derived by the following formula:

$$S.D. = \sqrt{\frac{\sum(x - m_1)^2 + \sum(x - m_2)^2}{n_1 + n_2 - 2}}$$

The mean error of the difference was derived by the following formula:

$$\epsilon = S.D. \sqrt{\frac{1}{n_1} + \frac{1}{n_2}}$$

The following values are found:

	S. D.	Mean error of the difference	Difference
Total lipids	90	53	38
Total cholesterol	19.4	11.4	11.8

The difference between the two groups is of no statistical significance. The two groups can therefore be added and the following mean values are found:

G1 + G3	Mean values of		Mean values increase	
	total lipids	total cholest.	total lipids	total cholest.
	397	72.7	150	31.1

The mean errors of the increase for both groups were 26 for total lipids and 5.6 for total cholesterol.

lipoprotein distribution during the period of the experiment were not so marked as in infants brought up on a normal diet. After the infants in group G1 had begun to receive an ordinary diet, the serum lipids and lipoproteins increased rapidly to the levels noted for infants receiving an ordinary diet all of the first days of life (see Table 19).

It is also apparent from Table 19 that, as long as an infant is on carbohydrate only, not only the serum lipids but also the relative distribution of the lipoproteins undergoes no change. As soon as the infant has got an ordinary diet, the lipoproteins rapidly assume a distribution seen in newborns brought up on an ordinary diet.

The distribution of combined and free cholesterol undergoes no remarkable changes during any of the experiments.

COMMENTS

It has been stated in this investigation that even in newborn infants, fed on a fat-poor milk diet, the serum lipids increase during the first few days of life. This was also shown to occur in infants on a synthetic diet consisting of carbohydrates and amino acids. The increase was, however, not so marked as in infants on an ordinary diet. This suggests that dietary fat contributes to the increase in serum lipids. The experiment showed about all that during the first days of life the endogenic fat metabolism is changed in such a manner that the serum lipids increase. This increase of serum lipids is reflected in the change in the distribution of the lipoproteins with an increase in the β -lipoproteins in the same way as in infants brought up on an ordinary diet. That the normal composition of the diet is of significance in the physiological increase of the serum lipids after birth was demonstrated by these cases in which the infants had received an ordinary diet at the end of the experiment and then the serum lipids and lipoproteins rapidly reached these values found in newborns brought up on an ordinary diet.

Of great interest are these cases in which the infants received only carbohydrates during the first few days of life. In these the serum lipids did not increase, nor did the relative percentage of the various lipoprotein fractions undergo any changes. One might be

tempted to assume that the lack of proteins in the diet might be responsible for this. It has been shown (RUSS, EDER & BARR, 1951), that the amount of protein is related to the lipid content in the lipoprotein fractions. In the newborn infants the marked increase in serum lipids during the first few days of life is accompanied by an increase in α - and β -globulins (MOORE, DU PAN & BUXTON, 1949, RAFSTEDT & SWAHLN, 1954). MOORE et al. suggested that the colostrum might be the cause of this increase.

It has, however, been shown that prolonged fasting is accompanied by hyperlipemia. In a series of four subjects KARTIN, MAN, WINKLER & PETERS (1944) found that the ingestion of 100 gm glucose, which corresponds to only 25 per cent of the energy production under basal metabolic conditions, is sufficient to prevent such hyperlipemia. In one subject, who had fasted for 6 days, they found the ingestion of glucose at the end of that period to be followed within 24 hours by an appreciable decrease in hyperlipemia. POSBORG PETERSEN (1952) found that the intake of glucose after 7 days fasting was followed by a decrease in the phospholipids within 3 hours. He claimed that it was hardly justified to assume that hyperphospholipemia during fasting is due to increased fat combustion, but should be regarded rather as an expression of the lack of carbohydrates in the intermediate metabolism.

It is evident from the literature mentioned above that not only the lack of protein but also the excess of carbohydrates in the feeding experiments with only carbohydrates in this investigation may play a role in the prevention of the ordinary increase in serum lipids. The findings in this investigation suggest that the better balanced a diet is in satisfying the requirements of the newborn infant the better will be its adaptation to extra-uterine life.

SUMMARY

In newborns the serum lipids increase even when the infant is fed on fat-poor citrido milk or a synthetic diet consisting of sugar and amino acids, although the increase is not so marked as in infants fed on ordinary diet. Even the changes in the relative lipoprotein distribution with an increase of β - and a corresponding decrease of

α -lipoproteins are seen in these infants. This infers that although dietary fat may contribute to the increase in the serum lipids during the first few days of life, this increase may be ascribable mainly to the changes of the endogenic fat metabolism.

In newborns fed on carbohydrates the serum lipids do not increase, nor does any change occur in the lipoprotein distribution during the first few days of life.

When the infants in these experiments received ordinary diet after the test period, the serum lipids and lipoproteins rapidly reached those values found in newborns brought up on an ordinary diet from birth.

Table I. Serum lipids in newborn infants fed on amino acids and sugar the first days after birth

Case No.	Sex	Age	Weight	Total lipids	Total cholesterol	Ester. cholesterol	Free cholesterol	Phospholipids	Remarks
150	F	At birth	3180	300	90	55	35	150	Fasting
		3 days	3140	360	104	64	40	160	After am.+sugar
		6 "	3320	580	152	94	58	170	After feeding with citrido milk
151	M	At birth	3280	420	87	62	25	134	Fasting
		4 days	2900	610	120	80	40	192	After am.+sugar
		7 "	3300	470	83	53	30	170	Fasting 19 hours
152	M	At birth	3300	660	131	88	43	224	After am.+sugar
		3 days	3050	660	131	88	43	224	After feeding with citrido milk
		7 "	3300	770	146	90	56	220	After feeding with citrido milk
153	M	At birth	3210	450	81	49	32	140	Fasting
		3 days	2900	590	94	54	40	180	After am.+sugar
		6 "	3650	550	90	61	29	156	After feeding with citrido milk

Table 15. *Serum lipoproteins in infants fed on amino acids and sugar the first days after birth*

Case No.	Sex	Age	Weight	Total lipids	α -fraction	β -fraction	Start fraction	Remarks
150	F	At birth	3480	303	129	93	78	Fasting
		3 days	3140	360	151	119	90	After am.+sugar
		6 "	3320	380	168	284	128	After feeding with citrido milk
151	M	At birth	3280	420	160	143	117	Fasting
		4 days	2909	610	165	305	140	After am.+sugar
		7 "	3300	470	212	127	131	Fasting
152	M	At birth	3300	470	212	127	131	After am.+sugar
		3 days	3050	660	264	231	165	After feeding with citrido milk
		7 "	3300	770	262	308	200	Fasting
153	M	At birth	3210	450	158	153	139	After am.+sugar
		3 days	2900	590	183	236	171	Fasting
		6 "	3600	370	174	126	70	After am.+sugar
154	M	At birth	3950	370	189	151	90	Fasting
		3 days	3650	330	215	220	115	After feeding with citrido milk

Table 16. Serum lipids in newborn infants fed on sugar the first days after birth

Case No.	Sex	Age	Weight	Total lipids	Total chol.	Ester chol.	Free chol.	Phospholipids	Remarks
161	M	At birth	3490	360	73	42	31	150	Fasting
		3 days	3300	420	84	—	—	140	After sugar feeding
162	M	At birth	3410	330	62	32	30	130	Fasting
		5 days	3150	350	70	36	34	136	After sugar feeding
		11 "	3500	520	133	86	47	212	After feeding with citrido milk
163	M	At birth	3510	400	76	50	26	140	Fasting
		3 days	8260	380	69	42	27	122	After sugar feeding
		5 "	3300	650	109	67	42	200	After feeding with citrido milk
164	F	At birth	3300	350	84	48	36	144	Fasting
		4 days	3030	350	83	51	32	168	After sugar feeding
		6 "	3120	530	131	82	49	230	After feeding with citrido milk
165	F	At birth	3010	350	79	40	39	182	Fasting
		4 days	2720	380	84	43	41	184	After sugar feeding
		5 "	2870	580	119	62	57	242	After feeding with citrido milk
166	F	At birth	3120	380	87	52	35	182	Fasting
		3 days	2880	360	79	42	37	208	After sugar feeding
		4 "	2920	170	109	60	49	240	After feeding with citrido milk
167	F	At birth	2500	320	69	40	29	144	Fasting
		3 days	2380	340	75	43	32	146	After sugar feeding
168	M	At birth	3730	290	77	44	33	161	Fasting
		3 days	3120	370	90	54	36	180	After sugar feeding

Table 17. *Skin oil proportions in newborn infants fed on sugar (in g.) after birth.*

Case No.	Sex	Age	Weight	Total lipids	α -fraction	β -fraction	Start-fraction	Fasting	After sugar feeding
161	M	At birth	3490	360	1.44	97	119	Fasting	After sugar feeding
		3 days	3500	420	1.51	1.43	126		
162	M	At birth	3410	330	1.78	89	63	Fasting	After sugar feeding
		5 days	3150	350	1.56	1.12	82		
		11 "	3500	520	1.35	296	89		
163	M	At birth	3510	400	212	116	72	Fasting	After sugar feeding
		3 days	3260	380	1.83	106	91		
		5 "	3300	650	1.95	267	188		
164	F	At birth	3300	350	1.12	123	115	Fasting	After sugar feeding
		4 days	3030	350	1.22	133	95		
		6 "	3120	530	1.22	297	111		
165	F	At birth	3010	350	1.47	112	91	Fasting	After sugar feeding
		4 days	2720	380	1.52	114	114		
		5 "	2870	580	1.28	302	150		
166	F	At birth	3120	380	1.71	118	91	Fasting	After sugar feeding
		3 days	2880	360	1.90	94	76		
		4 "	2920	470	160	212	98		
167	F	At birth	2500	320	1.89	74	57	Fasting	After sugar feeding
		3 days	2380	310	1.97	85	58		
168	M	At birth	3730	290	1.25	87	78	Fasting	After sugar feeding
		3 days	3420	370	133	118	89		

Table 18. *Serum lipids in newborn infants fed on skimmed citrido milk the first days after birth*

Case No.	Sex	Age	Weight	Total lipids	Total chol.	Ester chol.	Free squal.	Phospho-lipids	Remarks
171	M	At birth	3270	530	73	47	26	160	Fasting 22 h.a.b.
		4 days	3100	560	86	51	35	176	After skinned c.m.
172	M	At birth	3620	420	64	36	28	112	Fasting
		3 days	3460	570	83	47	36	128	After skinned c.m.
173	M	At birth	3830	540	64	40	24	140	Fasting 20 h.a.b.
		3 days	3600	740	98	49	39	160	After skinned c.m.
		11 "	3820	770	108	75	33	156	After citrido milk
174	F	At birth	4650	240	57	34	23	112	Fasting
		4 days	4300	330	91	52	39	170	After skinned c.m.
		11 "	4320	540	121	79	42	176	After citrido milk
175	F	At birth	3170	270	76	44	32	120	Fasting
		4 days	3040	370	101	62	39	134	After skinned c.m.
		At birth	4340	360	62	39	23	102	Fasting
176	F	3 days	4080	630	138	83	50	216	After skinned c.m.
		At birth	3120	403	80	50	30	100	Fasting
		3 days	2950	720	131	81	50	130	After skinned c.m.

Table 19. *Serum lipids and lipoproteins after feeding different kinds of food during the first few days of life*

Group		Time	No. of cases	Total lipids	Total cholesterol	Phospholipids	α -lipoprot.	β -lipoprot.	Start fraction
Carbohydrate+ amino acids	G 1	Fasting	5	40.2	79.2	143	166	128	107
		After 3 day's feeding	5	53.0	103.4	179	190	208	131
		After normal food	3	63.3	129.3	182	215	271	148
Carbohydrate	G 2	Fasting	8	34.8	75.6	155	160	102	86
		After 3 days' feeding	5	36.9	79.2	161	161	117	91
		After normal food	5	55.0	120.2	225	148	275	127
Skimmed citroo milk	G 3	Fasting	7	39.1	68.0	121	—	—	—
		After 3 days' feeding	560	105	159	—	—	—	—
		At birth	15	31.3	7.4	124	134	103	77
Normal		After 4 days' feeding	608	13.4	207	194	277	138	

GENERAL SUMMARY

In an investigation of the serum lipoproteins in infancy and childhood, in which attention was also directed to the total lipids, total and free cholesterol and phospholipids, and in which use was made of micromethods permitting the performance of all these analyses on 0.6 ml serum and thus even on newborn premature infants, the following observations of interest were made.

1. In serum from umbilical cord blood the total lipid, the total and free cholesterol and the phospholipid levels were much lower than in serum from normal adults.
2. In serum from umbilical cord blood the α -lipoproteins represented about 43 per cent and the β -lipoproteins about 33 per cent of the total lipids as against 30 per cent and 50 per cent respectively in normal adults.
3. During the first 12 hours of life the total lipids, total and free cholesterol and phospholipids increased by about 10—15 per cent, an increase possibly due to a dehydration of the blood during the first postnatal hours, during which no changes occur in the lipoprotein distribution.
4. During the first few days of life all the serum lipids increased steadily and on the fourth day they reached levels 80 to 90 per cent higher than at birth.
5. During the first few days of life the increase in the serum lipids was accompanied not only by an absolute increase in the lipoprotein fractions, especially of the β -lipoproteins (more than 100 per cent), but also by a marked change in the ratio between the α - and β -lipoproteins, the α -lipoproteins on the fourth day representing 29 per cent and the β -lipoproteins 46 per cent of the total lipids, a distribution corresponding roughly to that found in normal adults, in whom, however, the serum lipid levels are higher.
6. The ratio of the combined to free cholesterol in serum from umbilical cord blood (1.3 to 2.3) was below the normal adult range

(2.3 to 3.1) and remained so during the first few days of life, when the combined and the free cholesterol increased in absolute amount.

7. The cholesterol-phospholipid quotient in serum from umbilical cord blood was about 0.60 and increased to about 0.65 during the first few days of life (normal adult quotient: about 0.90).

8. The values found for newborn infants delivered by Caesarian section did not differ from those found for infants delivered by the normal route.

9. After the first few days of life successive analyses of specimens from the same infants during the rest of the first year of life showed that the values for serum lipids and lipoproteins fluctuated with a slight tendency to increase toward the end of the first year.

10. The ratio of the combined to free cholesterol also showed an increase towards the end of the first year to approach that for normal adults, the cholesterol-phospholipids quotient for the first year being on the average 0.70 and thus lower than in normal adults.

11. In children (2—14 years) the serum lipids and lipoproteins were higher than for the infants and fell within the adult range.

12. The ratio of the combined to free cholesterol and the ratio of the total cholesterol to phospholipids were higher for the children than for the infants and approach those for normal adults.

13. Serum lipids and lipoproteins in umbilical cord blood from premature infants were not found to differ from those found in fullterm infants. However, the serum lipids and lipoproteins did not increase so fast as in fullterm infants, but after about the first month of life no difference was demonstrable between the serum lipid and lipoprotein levels of the premature and fullterm infants.

14. Enzygotic as well as dizygotic twins of one and the same pair did not differ with respect to the serum lipid and lipoprotein levels of umbilical cord blood, but differences were found between blood samples collected a few days after birth.

15. In infants on a fat-poor diet as well as in those on a synthetic diet consisting of carbohydrates and proteins the serum lipids and lipoproteins did not increase so much during the first few days of life as in infants on an ordinary diet. The changes in the relative lipoprotein distribution were not so marked as in infants on an ordinary diet.

16. In newborns fed on carbohydrates only, the serum lipids did not increase, nor did any change occur in the relative lipoprotein distribution during the first few days of life, but as soon as the infants received an ordinary diet, the serum lipids and lipoproteins rapidly reached values found in newborns brought up on an ordinary diet from birth.

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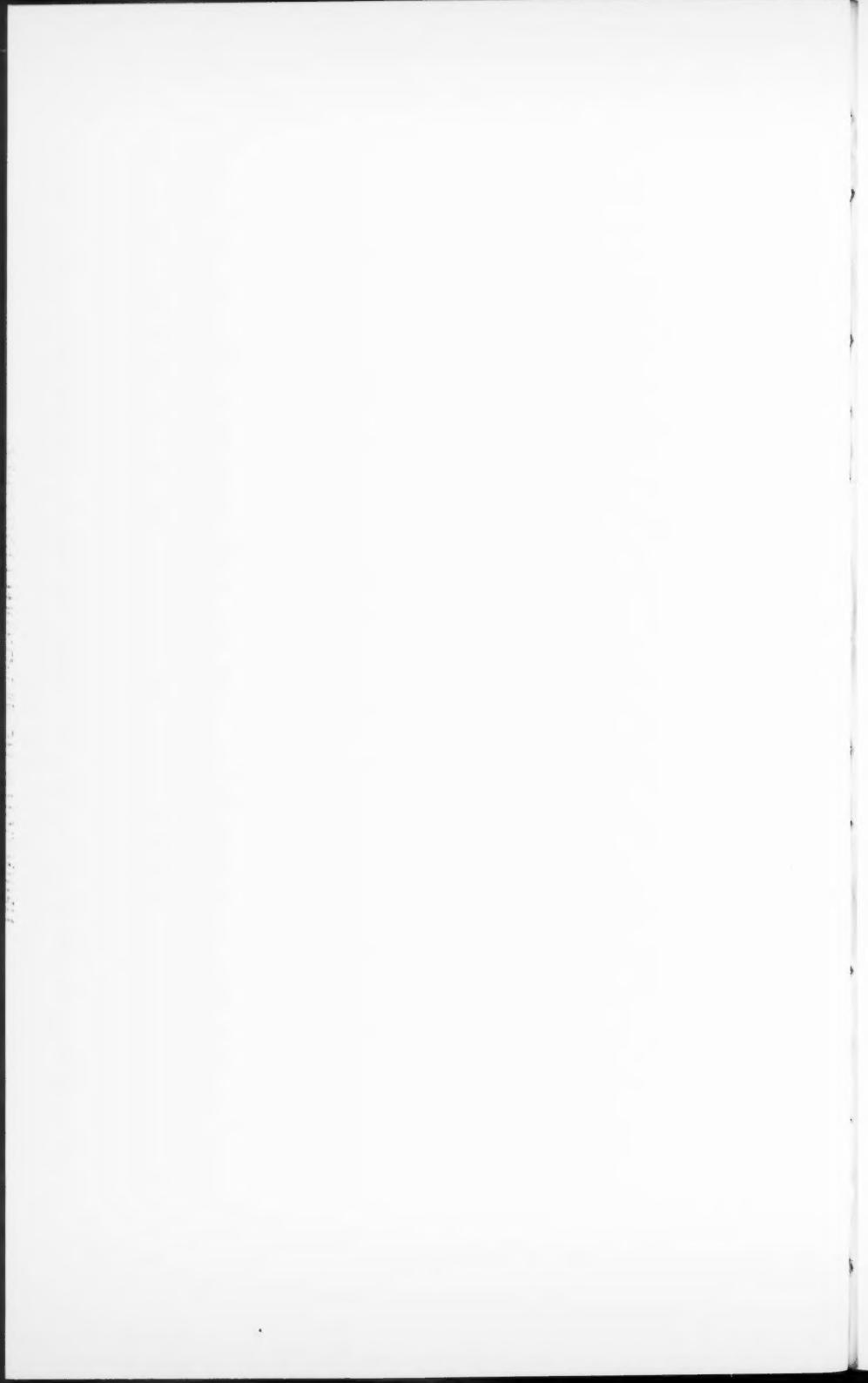


THE PROCEEDINGS
OF THE ELEVENTH NORTHERN
PEDIATRIC CONGRESS

OSLO · JUNE 28-JULY 1, 1954

Edited by
ARNE NJÅ
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CHEMICAL MEDICAL AND TECHNICAL



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Minutes of the Proceedings

Tuesday, June 29th, 9 a.m.

The President, Professor LEIF SALOMONSEN, opened the Congress. He proposed as Vice-Presidents:

Prof. P. PLUM, Copenhagen, Prof. T. SALMI, Helsinki, Prof. S. SIWE, Lund, Prof. A. SUNDAL, Bergen.

Section I

Tuesday, June 29th, 9.30-12 a.m.

Prof. L. SALOMONSEN took the chair.

Main Topic of the Discussion: Cerebral palsy.

Main Speakers: LEIF SALOMONSEN and MARIT SKATVEDT, Norway. PREBEN PLUM, Denmark.

Collaborators:

SVEN BRANDT, Denmark: Cerebral palsy and the pediatrician. His missions and his limits.

BJARNE ANDERSEN, Norway: Incidence of cerebral palsy in Norway and some c.p.-problems.

MARIT SKATVEDT, Norway: The electroencephalographic findings and the problem of epilepsy in a cerebral palsy material of 320 patients.

BENTE ERIKSEN, Norway: Intelligence tests in children suffering from cerebral palsy.

Section II

Tuesday, June 29th, 2 p.m.-4 p.m.

Prof. P. PLUM took the chair.

Main Topic of the discussion: Body water compartments and fluid metabolism in children.

Main Speakers: BENT FRIIS-HANSEN, Denmark. NIILU HALLMAN, Finland.

Collaborators:

JØRGEN VESTERDAL, Denmark: The renal excretion of water and electrolytes in infants.

LEENA TUUTERI, Finland: Circulatory disorders in acute dehydration.
HILKKA TÄHKÄ, Finland: On adrenocortical hormones in various diseases causing dehydration in infants.

M. SULAMAA and HANS TALLQVIST, Finland: Indications for fluid therapy in connection with surgical manipulations.

Section III

Wednesday, June 30th, 9-12 a.m.

Round Table Conference: The possibilities of diagnosing congenital heart disease by physical tests.

Leader: EDGAR MANNHEIMER, Sweden.

Collaborators: IB BOESEN, Denmark. LARS ERIK CARLGREN, Sweden. GUNNAR EKSTRÖM, Sweden. ODD HUSOM, Norway. BENGT JONSSON, Sweden. BERNHARD LANDTMANN, Finland. TAGE MÖLLER, Sweden.

Section IV

Wednesday, June 30th, 2 p.m.-5 p.m.

Prof. T. SALMI took the chair.

MARJATTA KUNNAS, Finland: Follow-up study of children, whose mothers had toxæmia of pregnancy.

YNGVE ÅKERREN, Sweden: Icterus neonatorum prolongatus indicating an early diagnosis of congenital myxedema.

M. d'AVIGNON, Sweden: The prognosis of congenital hypothyreosis.

JÖRN DITZEL, PRISCILLA WHITE, and JANINE DUCKERS, Denmark: The incidence of diabetes in children of young diabetic mothers.

OLE WASZ-HÖCKERT, Finland: Do vaccinations change the immunisation stability?

SVEN BRANDT, MAZAR DE LA GARDE, and TH. ROSENDAL, Denmark: The technique of pneumoencephalography in children.

BO HELLSTRÖM and L. GYLLENSTEN, Sweden: Changes in the eye similar to retroental fibroplasia induced by exposure of new-born mice to concentrated oxygen.

SVEN BRANDT and S. BILLE, Denmark: Treatment of petit mal with Dimedion, Tridione, Paradione and Milontin.

RAGNAR BERFENSTAM, Sweden: Causal relations in accidents to children.

SVEN BRANDT, Denmark: Film showing cataleptic seizures of hysterical or simulatory character in a 7-year-old epileptic boy.

Section V

Thursday, July 1st, 9-12 a.m.

Prof. A. SUNDAL took the chair.

Main Topic of the discussion: Asphyxia neonatorum.

Main Speakers: E. K. AHVENAINEN, Finland. WILHELM BLYSTAD, Norway. ROLF ZETTERSTRÖM, Sweden.

Collaborators:

SIINTO JÄYKKÄ, Finland: On the combined effect of circulation and respiratory movement during lung expansion by a new-born.

RAGNAR BERFENSTAM, L. ZETTERGREN and T. EDLUND, Sweden: Some facts concerning the pathogenesis of hyaline lung membranes.

B. LANDTMANN and E. K. AHVENAINEN, Finland: Electrocardiographic studies in asphyxia neonatorum.

BJÖRN WESTIN and GÖRAN ENHÖRNING, Sweden: An experimental study of the human fetus with special reference to asphyxia neonatorum.

YNGVE ÅKERRÉN, Sweden: Which method should be chosen for the treatment of asphyxia?

KURT HOLMDAHL, Sweden: The practical organization for the care of asphyxiated infants in the maternity clinics in Gothenburg, Sweden.

Presidential Address at the Eleventh Northern Pediatric Congress

On behalf of the Norwegian Committee of the Northern Pediatric Society, it gives me great pleasure to welcome to Oslo and to the XIth Northern Pediatric Congress, all the delegates from our four Nordic countries.

It is a special honour and pleasure to be able to extend a welcome to representatives from our countries' legations in Oslo, from the University of Oslo, and from the Oslo Municipal Authorities.

To the representatives of firms and companies who are taking an active part in our congress with exhibitions and advertisements I also extend a word of welcome, thanking them at the same time for the economic support they thereby contribute and which has made possible the execution of our arrangements for this congress.

Unfortunately, none of our Honorary Members have found it possible to be present at this congress. These members are Professor AF KLERCKER, Lund, Professor S. THORLING, Uppsala, and Professor WILHELM WERNSTEDT, Stockholm, and I ask permission to send these gentlemen a greetings telegram. At the same time I wish to inform the assembly that at a committee meeting of the Northern Pediatric Society yesterday it was resolved that as new Honorary Members of our Society the following outstanding representatives should be proposed: Dr. CARL FRIDERICHSEN, Denmark, Professor ARVO YLPPÖ, Finnland, Professor ARVID WALLGREN, Stockholm, and Dr. ARTHUR COLLETT, Norway. All of these have made a positive contribution to our Society and to previous congresses. (Applause)

I take the assembly's applause as an expression of their agreement to the Committee's proposal.

Unfortunately, we miss amongst us to-day Professor YLPPÖ, who is prevented by illness from being here. I would suggest that we also send him a greetings telegram.

Since our last meeting in Stockholm, three years ago, many of our members have died.

Professor C. E. BLOCH died on February 11th 1952, at the age of 79. Professor Bloch was President of the 1st Northern Pediatric Congress in 1919. Measured by international standards he was one of our times most outstanding pediatricians, and his death has meant a great loss to Scandi-

navia. Realistic as he was, and possessing great clearness of thought, he was the perfect teacher, and a clinical research worker of great dimensions. In this connection it suffices to mention his discovering that xerophthalmia is caused by a lack of vitamin A. He also possessed considerable organizational and diplomatic qualities, which, not the least during the war, were of great benefit to the University of Copenhagen. Our Society expressed its respect for Professor Bloch at our congress in 1948 when he was created an Honorary Member.

Denmark suffered another great loss in the same year with the death of VALDEMAR POULSEN, a loss which, to a great extent, affects our inter-Scandinavian congresses. At these Valdemar Poulsen was, for many years, a faithful delegate. He was for a long period a member of the Danish Committee in our Society, and with his friendliness and charm, he contributed greatly to the success of our meetings. His personality left its mark on his hospital at Fuglebakken, where he created a special atmosphere of friendliness and confidence. He has rendered important service to research, especially within the field of tuberculosis, and in spite of the fact that his principal interests did not lie in the field of scientific research. It suffices to mention his experiments on the detection of the tubercle bacillus in lavage contents of the stomach.

We deeply regret the deaths of other Danish colleagues: AAGE BOJESEN, KAJ TRIER, and ELISABETH SVENSGAARD.

From Finnland we have received the sad news of the death of Medical Advisor JOHANNES CARPÉN, and from Sweden the deaths of GÖRAN NORDENSON, EINAR BELFRAGE, and DAVID LINDSJÖ.

In Norway FINN ARNESSEN and KAREN MARGRETHE SIMONSEN have died. The Danish-born KAREN MARGRETHE SIMONSEN died on May 13th 1953, only 49 years of age. She came to Norway in 1950 as the first Head Doctor of our first Children's Psychiatric Ward. She came with fresh and enthusiastic desire for work to execute the demanding task which lay before her: to give this new and young field in medicine, Child Psychiatry, a sound start here in Norway. Doctor Simonsen possessed that happy combination of personal qualities which this task called for. Despite the fact that her work here in Norway came to an end after only three years, it was of great fundamental value, and it will bear fruit far into the future. She built up our first Children's Psychiatric Ward. She laid the foundations of the teaching of Child Psychiatry at the University of Oslo, and, first and foremost, she carried this study through to be an independent, honorable and respected science within Norwegian medicine.

Let us honour our deceased friends' and colleagues' memories by standing a minute.

Ladies and Gentlemen:

Our century has been called the Children's Century. There are, however, other and important problems apart from the child's which engross human thought in this our uncertain and chaotic age. But amongst all the search-lights which are directed towards the great problems of our times, one is also directed towards the child. The understanding of its mental as well as its physical problems has, in the last century, been in the process of transformation in a revolutionary way. At the same time, the child, as a medical and social problem, has taken a much greater place in the conscience of the society than before. Thus, in our century Pediatrics has, as a study, become of increasing importance, and from a modest speciality developed to become one of the central studies in medicine.

Northern Pediatric research has made an active contribution towards the clarification of the many problems within Pediatrics. In the first instance our Northern congresses shall be a manifestation of these contributions, a manifestation of the pediatric standard here in Scandinavia, and a manifestation of what Scandinavia's Pediatricians are. If we take a forest as a symbol of this manifestation we will see that even the trees grow old and that many of them fall. But new ones grow up. Some are lofty, reaching up into the heights. Others expand in breadth. And then there are the saplings. The Congress' task is to guard this our pediatric forest, keep it clear of wild growth, and give it a fertile soil so that its healthy growth be stimulated. We wish for no peaceful forest, no dense, quiet forest, but a free forest, blown by the fresh winds of Science.

But our congresses should also have another aim. Scientific development of our subject, as in others within the field of medicine, is so strong, so ever increasingly strong, that it is continually more difficult for the pediatrician to keep himself *à jour* with the progress being made. It can also be difficult for the pediatrician to estimate the new tendencies and new developments which emerge, difficult to distinguish the valuable new from the less valuable. In addition to giving a special manifestation of the scientific standard within Northern Pediatrics, an important aim of our congresses ought to be an attempt to give an outline of the international progress made in recent years within our field, and to give an estimation of the importance of such progress.

If we were to give the active delegates to our congress a free choice of subjects on which to lecture, the time we have at our disposal for the congress would not be sufficient for us to give such an outline. I fear that we would drown in the multitude of the subjects chosen. It will undoubtedly be of greater value to those listening that we limit ourselves to certain set themes, and to go into greater detail within these. This is the reason for

the fact that at this congress we have strictly limited the time for lectures given on freely chosen subjects, and, instead, taken up definite themes for discussion.

The choice of these themes has been reached after consultation with the heads of the Northern University Clinics. In the fields which have been chosen, fruitful and intense research has been carried out the world over, and this seems to point towards results which can be of the utmost importance for the reduction of illness and death amongst children. This concerns the most frequent cause of death amongst newly born children, asphyxia neonatorum, where a clarification of the pathophysiology will be decisive in order to arrive at a reduction of the risk of death for the child in connection with its birth. It also concerns cerebral palsy, this old, well-known disease, which suddenly has come into the limelight, because new possibilities for its prevention and cure are now visualised. It also concerns the new knowledge of the ability to counter-act the complicated disturbances of electrolyte equilibrium in states of dehydration in infants.

Finally it embraces congenital diseases of the heart, which have come into the limelight again through the possibilities of modern surgical treatment. Because of its demanding diagnosis pediatric cardiology threatens to divorce itself from pediatrics and become a special field of study. Our object in bringing it forward for discussion is to try to keep it within pediatrics by showing what the ordinary pediatrician can do with his eyes, his hands and his stethoscope in the diagnosis of the congenital heart diseases.

The time for our proceedings has now arrived. After the proposals made at yesterday's committee meeting I suggest the following delegates as Vice-Presidents of the Congress: Professor PLUM, Denmark, Professor SALMI, Finland, Professor SIWE, Sweden, and Professor SUNDAL, Norway.

In the hope that this congress will fulfill its aims: a rich scientific harvest, a fruitful exchange of ideas, and a genial reunion of colleagues, all to the good of Pediatric's further growth in Scandinavia, I declare the XIth Northern Pediatric Congress open.

SESSION I

Cerebral Palsy

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The Clinical Features and Etiology of Cerebral Palsy

by LEIF SALOMONSEN and MARIT SKATVEDT, Norway

The usual classification of cerebral palsy in four sharply defined types distinguished by spasticity, athetosis, rigidity and ataxia respectively is not quite satisfactory. The remarkable differences of opinion among various authors with respect to the relative frequency of these clinical types are partly due to diagnostic difficulties, but also to the fact that the clinical manifestations do not always occur in a pure form, but very often there is found in one individual a mixture of neurological phenomena belonging to various types.

In view of the demonstration in recent years of the intimate anatomical and functional connections between the pyramidal and extrapyramidal systems, it is not surprising to find symptoms referable to both these systems in one and the same patient. With the exception of the spastic hemiplegias, the lesion in most cases of cerebral palsy is probably situated deeply in the centre of the brain and localised to the area supplying v. Galeni magna and its branches. A vascular lesion in this area involves both the basal grey nuclei and the pyramidal tracts where they run between these nuclei in the capsula interna. The reason why the manifestations of cerebral palsy are so often bilateral and symmetrical is to be found in the fact that damage to this centrally situated vascular system must affect both sides equally.

The following findings serve to substantiate our contention that damage causing cerebral palsy in many cases is deep-seated: In 48 children with various forms of cerebral palsy we have found a definitely pathological *pneumo-encephalogram*. In 47 of these cases (98 %) changes were found situated deeply in the centre of the brain, very often in the form of dilatation of the third ventricle. This was also the case with patients presenting purely spastic symptoms.

Electro-encephalograms of 176 patients showed (with the exception of the spastic hemiplegias) that general dysrhythmia occurred much oftener than dysrhythmia starting from a cortical focus.

The clinical examination of 320 children suffering from cerebral palsy showed the following distribution of cases (see Table 1).

Table 1

	Pure spasticity		Pure atetosis	Pure ataxia	Mixed form (both extra-pyramidal and pyramidal symptoms)	Total
	Hemi- plegia	Bilat. spastic paresis				
Number	Absolute . . .	65	112	45	16	82
	Relative . . .	20.3 %	35 %	14.1 %	5 %	25.6 %
Intelli- gence	Normal . . .	7	34	18	6	6
	Reduced, but capable of training . . .	3	15	5	4	6
	Much reduced	3	14	0	2	38
Epilepsy	17	22	4	2	21	66

Table 2

Etiological factors in cerebral palsy

	Spasticity		Pure atetosis	Pure ataxia	Mixed form	Total
	Hemi- plegia	Bilat. spastic paresis				
Number of patients	65	112	45	16	82	320
Kernicterus			8		7	15
Prematurity	Weight at birth under 2,500 g of 266 infants					
	8	47	7	0	13	75
	Relative number	17 %	50 %	19 %	18 %	28 %
Information about asphyxia brain injury at birth	25	45	25	10	42	147
	Relative number	39 %	40 %	55 %	63 %	51 %
Course of labour in 301 cases	Normal	31	67	28	7	44
	Pathological . . .	29	35	15	9	36
	Relative number	48 %	34 %	35 %	56 %	41 %

In 25.6 per cent of our cases we could not classify them in any of the ordinary clinical types. These patients showed a preponderance of extra-pyramidal phenomena, with general rigidity, retardation of movements, reduced facial mimicry and at the same time in many cases athetoid movements or ataxia. There were also slight pyramidal tract manifestations in the form of somewhat increased reflexes, but without the typical extensor reflex of the antigravity muscles. The intelligence of these patients was relatively lower than was evidenced in the remaining cases.

It is, we suspect, this large group of patients which is included in the spastic group by some authors and in the athetotic group by others. And this is probably the explanation for the great variations in the relative frequency of the different clinical types.

The main problem raised by cerebral palsy concerns its prevention, and to this end we must be familiar with its *etiology*. This seems to be known only in a few cases, some 5 per cent which are due to kernicterus, and the spastic hemiplegias which are presumably due to a vascular lesion occurring during birth or later infectious, traumatic or other lesions involving one side of the brain.

But little is known of the etiology of the overwhelming majority of the bilateral, symmetrical forms of cerebral palsy. Three different etiological possibilities are:

1. Cerebral malformation of a genetic character.
2. Cerebral developmental inhibition caused by damage to the foetus in the embryonic period.
3. Cerebral damage incurred during the birth process.

The statistically significant findings (substantiated by our data given in Table 2) such as the frequent incidence of *prematurity* and of *asphyxia*, as well as of *cerebral symptoms* in the perinatal period cannot be used to establish the etiology of cerebral palsy. These conditions may be responsible for causing cerebral palsy, but they may also be the result of some cerebral defect existing before birth.

All three of these etiological possibilities may perhaps come into play, but in our opinion there are strong arguments for allocating a relatively subordinate role to the first two of them.

The rare occurrence of familial manifestations of the disease makes it difficult to relate it to a *malformation of a genetic character*.

In opposition to the possibility of *external embryonic injuries* being responsible, is, first and foremost, the absence of other malformations in the subjects of cerebral palsy since it is common for embryonic injuries to give rise to multiple malformations. Again, neither our own material nor the

materials presented by other observers have yielded data indicating an increased frequency of haemorrhage during pregnancy or of unusually great exposure of the mothers to harmful influences.

The main cause of cerebral palsy is, in our opinion, to be found in *anoxæmic brain necroses occurring during the birth period*. Several follow-up investigations of infants suffering from asphyxia at birth have been published. While some authors have demonstrated an increased rate of cerebral palsy in such infants, others have not been able to confirm this finding. These statistics cannot, however, have the last word in this matter because a clinical asphyxia does not cover all the anoxæmic injuries to the brain. An anoxæmic cell death may occur in parts of the brain which are dumb at birth without such an event betraying itself clinically as asphyxia because the more resistant centres in the medulla oblongata continue to function.

A strong argument in favour of the importance of perinatal damage to the brain is to be found in the statistically certain establishment of an increased incidence of *pathological births* among children suffering from cerebral palsy. In our material positive data on this score were recorded in 41 per cent, particularly with regard to breech deliveries and prolonged labour. In this connection a certain interest is attached to the finding in our material where a relatively great number of *large babies* (weighing over 4,000 g at birth) were evidenced.

Another strong argument is to be noted in *pathological-anatomical findings* (PH. SCHWARTZ, BENDA). These observers have drawn attention partly to the very great frequency of small haemorrhages and ischaemic necroses in the area supplied by the v. Galeni in the subjects of neonatal death, partly to post-mortem findings in cases of cerebral palsy. In the overwhelming majority of such cases, pathological changes are to be found in the same vascular area and are most likely to be traceable to ischaemic necroses which had developed earlier in the same area.

This venous system is particularly vulnerable in premature infants. The frequent combination of cerebral palsy and prematurity thus finds its natural explanation.

In view of these findings we may say that large groups of our cerebral palsy patients are children who have been in danger of perinatal death from asphyxia, but have evaded this death. The prophylaxis of cerebral palsy must have as its starting-point the large, unexplored field of research: the action of hypoxæmia on the brain cells during birth in the sublethal degrees of cerebral ischaemia.

Cerebral Palsy

by A. MØLHAVE and P. PLUM, Denmark

The pathophysiology of cerebral palsy is briefly described. As an example the statics and dynamic in a typical case of spastic paraplegia is described and analysed. A way to demonstrate the decreased ability to perform isolated movements is described. This demonstration is at the same time an examination of diagnostic value. The ability to perform the individual movements which constitute the components of the normal motor patterns is decreased or lacking. This dysfunction will often lead to dynamic and static deformities. If these are corrected passively the disability to perform certain isolated movements is accentuated. Therefore our physical exercise aims at increasing the ability to perform voluntary isolated movements in such postures in which the dynamic and static deformities are corrected. At the same time we try to improve the coordination and the ability to change the speed of movement. Further the exercises must aim at correcting abnormalities of muscle length; this can be done by exercising shortened muscles in extension, i.e. stretched as much as possible and vice versa.

Cerebral Palsy and the Pediatrician. His Missions and his Limits

by SVEN BRANDT, Denmark

Prevention and the early diagnosis and treatment are the fields where the pediatrician can use his special experience and knowledge. Mild cases can be cured and some moderate case improved so that normal school education may be followed. Many children with c.p. grow out of their childhood still more or less handicapped. C.p. is a pediatric disorder indeed—but it is at the same time a chronic abnormal condition in the nervous system. The pediatrician himself can only exceptionally cover all the different aspects of the diagnosis and treatment of c.p. Most of us will probably do our best in cooperation with other specialists. We must learn from others if we want to keep ourselves abreast with the development of our speciality, which is really a group of specialities in childhood.

At the c.p. department of the Society and Home for Crippled in Denmark, all diagnostic work is in the hands of a pediatrician with neurological training. The treatment is planned for each child in cooperation with the orthopedist and the different therapists. Surgery is rarely used, but we

feel that, like in pyloric stenosis, orthopedic surgical procedures may bring some children faster to a result than conservative training alone. We have realised, at the same time, that many operations made in earlier days, when the orthopedist was the only one interested in treatment of c.p., have failed. This applies first of all to the combined operations on nerves and tendons.

Some preliminary results of either physiotherapy and occupational therapy alone or combined with operations are demonstrated in a film. The organization of the c.p. treatment center of the Society and Home for Crippled Children, Copenhagen, is briefly described and demonstrated on a schematic figure.

Incidence of Cerebral Palsy in Norway and Some C.P. Problems

by BJARNE ANDERSEN, Norway

A study of the incidence of cerebral palsy in Østfold County, Norway, has been performed. The annual incidence of cerebral palsy is estimated at 3.6 cases per 100,000 of the total population, or 1.9 cases of cerebral palsy per 1,000 births. Taking the incidence in Østfold County as reflecting the incidence among the general population, the total number of cerebral palsied persons in Norway would be 7,600. Of these 2,300 are under the age of 21 years.

The incidence of mental defects was estimated at 49 per cent.

Speech habilitation seemed indicated in about 60 per cent of the cases over 3 years of age, feeble-minded patients not included.

The therapeutic approach concerning the problem in general was discussed.

(The paper is printed in the Journal of the Oslo City Hospitals, Vol. 4, No. 5-6, May-June 1954, p. 65-87.)

The Electroencephalographic Findings and the Problem of Epilepsy in a Cerebral Palsy Material of 320 Patients

by MARIT SKATVEDT, Norway

The material consists of 320 patients with cerebral palsy. Sixty-five had hemiparesis, 112 bilateral spasticity, 45 athetosis, 16 ataxia and 82 were

mixed pyramidalextrapyramidal cases. Electroencephalograms were recorded in 176 cases. Of these 41 per cent were normal, 59 per cent pathological. There was some correlation between normal recordings and less serious cases, but not conclusively since almost half of the most serious cases in the mixed group had normal EEG.

Three hemiplegics had general dysrhythmia, 1 had pathologic foci in both hemispheres and 1 had a pathologic focus on the "wrong" side of the hemiparesis. In bilateral spasticity some had general dysrhythmia, some several foci, but 1 patient had only a subcortical focus and 50 per cent of all patients in this group had normal EEG. Of the athetotics 3 had cortical foci, 1 subcortical, 12 general dysrhythmia. Two ataxic patients had cortical foci.

Our conclusion is that the EEG is normal in a surprising number of cases, but when the EEG is pathologic, it often shows that the damage to the central nervous system is more widespread than one would suspect from the clinical picture.

In 320 patients 66 (20.6 per cent) have had manifest epileptic seizures. Of the 176 patients in whom EEG is recorded, 48 have had seizures and 21 had epileptogenic foci without having had seizures up to this time (June 1954). If one adds the manifest and the potential epileptics of these 176 patients, one gets the figure of 38 per cent. The prematures (75 patients) had the same frequency of manifest epilepsy as the rest of the material, 20 per cent.

Of the 66 patients with manifest epilepsy 27 had only had one or a few seizures and needed no medicamental therapy; 5 spastic patients were sent to institutions for the mentally retarded without physiotherapy, 5 had died, 3 in status epilepticus, 4 patients had disappeared from control. A group of 18 have combined antiepileptic drugs and physiotherapy and are free from seizures and 3 are under adjustment on antiepileptic drugs. They tolerate physiotherapy well. In 3 hemiplegic patients physiotherapy seemed to induce seizures and had to be abandoned.

The antiepileptic drugs used have been the usual; we use phenobarbital and phenantoin combined a great deal. One athetotic patient had increased athetotic movements on phenobarbital, but phenantoin controlled his seizures without interfering with his control of the athetosis. In no other cases have there been complications with drug therapy.

Conclusion.—Epilepsy in cerebral palsy is rarely any hindrance to a successful physiotherapy, and the control of seizures by antiepileptic drugs is as good in these patients as in other epileptics. But in a few hemiplegic patients physiotherapy seemed to induce epileptic seizures.

Intelligence Tests in Children Suffering from Cerebral Palsy

by BENTE ERIKSEN, Norway

Between September 1, 1953 and April 15, 1954 a total of 67 children suffering from cerebral palsy were tested at the Rikshospital, Valstadbråten, Sagene Helsestasjon and Tomtebo.

It is probable that the result of these tests were not a measure of the children's maximum capacity.

The following tests were used: The revised Binet test, Terman Merrill form M., and the Arthur adaptation of the Leiter performance scale. The verbal element in Terman Merrill disqualifies it for use in children suffering from speech defects. Certain elements of the test requiring movements of the hands also disqualify them for application to children whose hands are subject to motor disturbances. In spite of these difficulties, I have succeeded in 47 out of 67 cases to test with Terman Merrill. The Binet scale is to a large extent derived from experiences observed in normal children at liberty to move freely and able to receive impressions and express themselves to those about them whether they are at home or in the playground. We must keep these facts in mind when forming an estimate of the score obtained by testing a child suffering from cerebral palsy. In 1940 Russel Graydon Leiter published a test which he thought could replace the Binet scale in the cases in which a verbal test could not be used. The test consists of placing blocks, of the same size and shape, so as to form a pattern or a system which a child may understand after having been shown a corresponding pattern or part of it. The Leiter test has certain advantages over a verbal test.

1. The scoring is entirely objective (the blocks are arranged either correctly or incorrectly, the conductor of the test never being left to form his own judgment).

2. More new material is used than in verbal tests. (The elimination of both speech and material already known to the child reduces to a minimum the influence of environmental factors.)

Most children are more interested in concrete than in verbal tests. In some cases great demands are made on the child's concentration and will-power when he must keep his head quiet and glance fixed on a series of drawings. The test cannot be applied to children with a visual handicap.

These results give a picture of the distribution of intelligence among those children who at the time of testing were living at our centres for the treatment of cerebral palsy.

The ages ranged from 3 years to (in 2 cases) 17 years, the mean age being 7 to 8 years. Can we compare I.Q. of a 4-year-old child with that of a 12-year-old child subjected to the same test? Follow-up studies of Terman Merrill have shown that I.Q. here is constant. With regard to Dr. Leiter's test, its scale is most useful and reliable for children from 5 to 12. Cases of spasticity, athetosis and ataxia are included in the material with spastic paresis predominating. The mixed group is not represented here.

We are confronted by the following when testing cerebral palsy children: They are abnormally sensitive to stimuli in their environment, and they let themselves be influenced passively and without any special objective in response to any sound or movement whatever.

As with all such testing it is very important that the child should sit in a calm environment, feeling physically well, whether resting in specially constructed chairs or lying down if this is necessary. As cerebral palsy children tire sooner than normal children, it is often necessary to distribute the testing over several days.

A characteristic feature often observed in these children is their dependence on help from others and their claiming to be noticed by grownups. In particular they are wide awake to signs and hints. The one who is testing has to remember this, having an intense wish that the child should have the chance to do its best. The answer is often so close to being correct. However, these children are in constant need of encouragement if they are not to give in.

In the book *Psychopathology of the Brain Injured Child* (STRAUSS and LEHTINEN) an account is given of divergencies in perception and thought in comparison with normal children. The book also contains a description of certain behavior disturbances observed with special reference to children whose brains were damaged. HOAKLEY has attempted to isolate the component elements of Terman Merrill form L which give results showing definite variations according as the brains of the children examined were or

Table 1

I.Q.	Number	Above normal 115	Normal 115-85	Re- tarded 85-75	Debile 75-55	Imbecile 55-35	Idiots < 35
Spastic diplegia .	37	2	24	4	5	2	
Spastic hemiplegia	11	0	4	3	4	0	
Athetosis	15	0	10	3	2	0	
Ataxia	4	0	1	1	0	2	
Total	67	2	39	11	11	4	

Table 2

(1)

Test used	Number childr.	Arithm. mean	St. deviation
Leiter	67	83.9	19.97
Terman Merrill . .	47	83.4	20.12

(2)

Test used	<i>Spastic paresis</i>			<i>Athetosis</i>		
	Number childr.	Arithm. mean	St. deviation	Number childr.	Arithm. mean	St. deviation
Leiter	48	84.75	19.47	15	87.83	13.62
Terman Merrill	40	86.5	11.09	4	76.75	—

were not damaged. The only element in this test showing a significant difference between the two groups was the visual, perceptual one of the "diamond drawing".

Here the grouping depends chiefly on the results obtained by the two tests Terman Merrill and the Leiter performance scale. In this investigation the correlation between the two tests was found to be .89. When the differences between the two testings were great, more importance was attached to the results of the Terman Merrill test when the examiner found it defensible to employ it. Special attention was paid to the child's physical handicap.

1. Twenty out of 74 children were tested only with the Leiter performance scale because of their difficulties in speech. In 7 cases it was impossible to evaluate the test result because of physical handicap or lack of cooperation. The low standard deviation (compared with other investigations of the distribution of intelligence in cerebral palsied children) may be due to the character of the material examined.

2. Four cases of athetosis were tested with Terman Merrill. For this reason it is difficult to calculate with a dispersion measure expressed as standard deviation. There appears to be no significant difference between the means for the two groups tested by the Leiter performance scale.

Discussion

M. d'Avignon, Sweden.—“Spastic” children in Sweden have since the end of the last century been treated in Eugeniahemmet in Stockholm. About 70 such patients are continuously under treatment. In recent years an increasing number of younger children have been admitted, but the majority of patients have been older children with severe spasticity with contractures and severe cases of athetosis. Because the diagnoses have not been made earlier, these patients have come late under treatment, this treatment being mainly orthopedic. To achieve an earlier diagnosis and subsequently a prompter treatment educational measures are necessary. With this aim in mind, 2 to 5 cases are always being treated in the Children's Department of the Karolinska Hospital. This hospital is an educational clinic not only for medical students, but for children's nurses and physiotherapists as well. Cases already diagnosed are sent from pediatricians throughout the country. The patients remain with their mothers 3-4 weeks in the children's department, where, when the cases have been scrutinized, they receive daily treatment by a physiotherapist working in the presence of the mothers to enable these to continue the treatment at home. The team which examines and treats the patients includes an orthopedic expert, a pediatrician, a neurologist when necessary, a child psychiatrist, a psychologist, a specially trained occupational therapist, and a hospital staff well familiar with the difficulties of such patients. The treatment of speech defects is in some cases started during the stay in the hospital, to be continued in the home. The patient is kept under supervision either at home or by later visits to the hospital. The State Board of Health has proposed an expansion of Eugeniahemmet in order to enable it to receive young children for early diagnosis and treatment. To the hospital will be attached a team of child psychiatrists, a speech expert, pediatricians and, when necessary, a neurologist in addition to the orthopedic expert and physiotherapists already available.

G. Herlitz, Sweden.—When we investigate the frequency of cerebral palsy, it would be advantageous to devote special attention to the children admitted to hospitals for the mentally defective. On closer scrutiny we may find among these children several cases of palsy which have hitherto been regarded as oligophrenics without the aetiology or type being specified. Such an oversight may possibly be one of the reasons why there are so few cases of incapacity for training in certain spastic materials.

It does not seem logical, as usually happens, to calculate the frequency of cerebral palsy in a given population by counting the number of palsy

cases born every year per 100,000 of the population, as a considerable number of palsy cases are recruited from among premature infants many of whom die before they have reached the age at which it is possible to find out the presence or absence of any central motor disturbance. In a 3-year material in Linköping there were 72 deaths among 275 premature infants weighing less than 2,500 g at birth. Among these 72 infants were 66 whose death occurred during the first week of life. Under such conditions it would be wiser to express the palsy frequency as a percentage of the survivors in the different age groups. In doing so it may perhaps be best to discount the first year of life when it may sometimes be quite difficult to arrive at a diagnosis.

In most spastic materials boys seem to outnumber girls, but as a rule the figures are too small to warrant the conclusion that this difference does not depend on chance. If, however, we run all the available figures together we shall find support for this sex difference. By extending our census of spastic cases in a given community so that it includes every mentally defective child whether it does or does not suffer from palsy, this sex difference becomes still more marked, at any rate with us in Östergötland with a population of 260,000. We do not know the explanation of this phenomenon. Personally it seems to me that the comparatively high mortality of male infants in relation to female infants is reflected in an increased vulnerability of the central nervous system among other structures in the boys who survive. (It should be noted that 106 boys continue to be born for every 100 girls; this sex difference is said to be even greater at an earlier foetal stage.)

C. E. Räihä, Finland.—With regard to any prophylactic measures it would be well to consider certain preliminary investigations into the tissue metabolism in nerve tissues. We know that the sugar consumption varies in different parts of the brain and during different stages of its development. In young animals more sugar is consumed in the brain stem than in the brain itself, the reverse being the case in later stages of development. The oxydative enzyme systems also undergo a certain development. Cytochrome increases with age and reaches a higher level in mature than in premature infants. RICHARD DAG has shown that acid consumption in a tissue preparation diminishes considerably if bilirubin is added to the nutrient solution, and that this inhibition is prevented by cytochrome. There may be some correlation with the tendency to develop kernicterus which is characteristic of premature infants.

SESSION II

The Electrolyte Balance

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Body Water Compartments and Fluid Metabolism in Children

by BENT FRIIS-HANSEN, Denmark

Interest in body fluids has existed since ancient time. In the "humoral pathology" the Greeks have ascribed all diseases to some want of balance of the body fluids, and water itself was considered as one of the four elements in nature.

Up through historical time spas have played an important role, but the first important step was taken in 1831 when the English Dr. LATTA gave an intravenous injection of a slightly hypotonic solution of sodium chloride and sodium bicarbonate to a dehydrated patient, with excellent results.

This revolutionary therapeutic advance was soon forgotten, and during the later part of the last century interest was focussed on the mineral composition of the body in health and disease, but the subject was somewhat obscured by the introduction of the term "intestinal intoxication" by FINKELESTEIN instead of the more descriptive "dehydration".

Fundamental knowledge of the characteristics of body fluids has been attained in the twenties and thirties, first of all by GAMBLE, and the introduction of potassium in therapy was made by DARROW.

The first slide (Fig. 1) is a diagrammatic presentation of body composition, and the next (Fig. 2) illustrates how *total body water* decreases from 80 per cent at birth to some 60 per cent of body weight at one year of age. *The extracellular fluid* comprises 45 per cent at birth, decreases to around 25 per cent at one year, whereafter a slight decrease is noted to around 20 per cent at puberty. *The intracellular fluid* increases during the first month of life from 35 to 40 per cent and then remains fairly constant.

In cases of emergency water is stored in or drawn from the muscles and the subcutaneous tissues.

The composition of extracellular fluid, interstitial and intracellular fluid is discussed and the diagram of GAMBLE is shown.

The cells are surrounded by extracellular fluid as illustrated on Fig. 3. The normal composition is maintained primarily by the lungs and the kidneys under humoral and neurogenic control. The antidiuretic hormone increases the reabsorption of water in the kidney. The effect of the "electrolyte hormone" of the adrenals is paradox since the direct effect is increased

BODY COMPOSITION

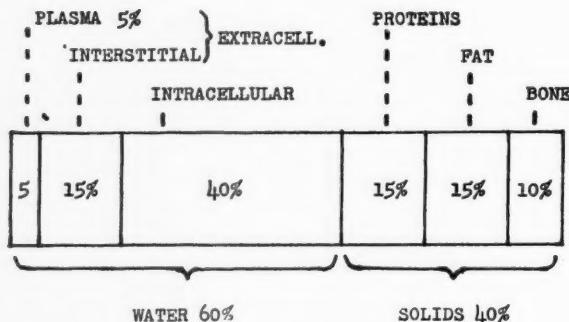


Fig. 1.

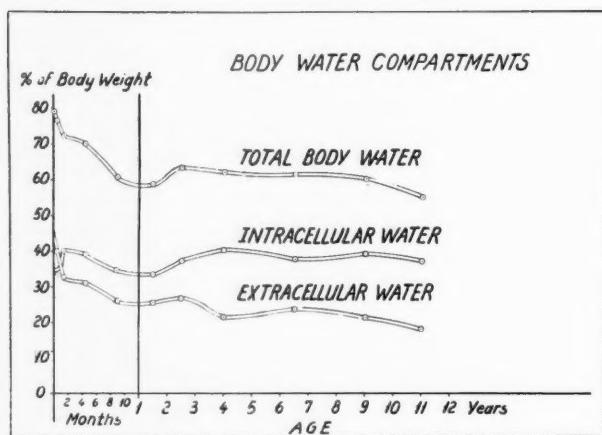


Fig. 2.

diuresis, but as another effect is sodium retention, the overall result may often be a water retention.

Many theories have been put forward to explain the separation of extracellular sodium and potassium inside the cells.

First impermeability of and later pores in the cell membrane were believed to be the cause, but as this has been disproved, the cell membrane has been assumed to have a pump-like function that either pumps sodium out of the cells or potassium into the cells.

The finding that certain mitochondria have the ability to concentrate sodium some fifty times is in favour of the sodium-pump theory.

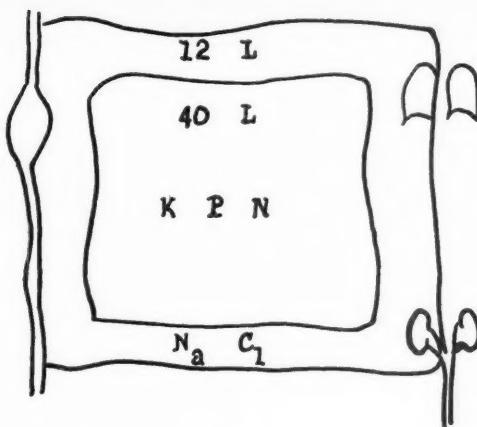


Fig. 3.

Body Water
Infant 6kg

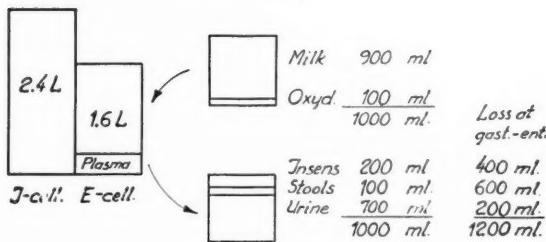


Fig. 4.

It has been shown lately that the hydrated sodium ion is several times larger than the hydrated potassium ion, and it has been postulated that the structure of the proteins of the cells is such that the distance between the branches of the protein molecules is so small that it is impossible for the sodium ion to enter the small spaces.

An important antagonism exists between sodium and potassium. Large doses of sodium will induce a potassium loss from the organism, and this is one reason for a careful dosage of sodium to patients.

Fig. 4: The daily *water metabolism* of an infant. The turnover represents $\frac{2}{3}$ of the extracellular fluid or $\frac{1}{4}$ of the total body water.

K-Pool
Infant 6 kg

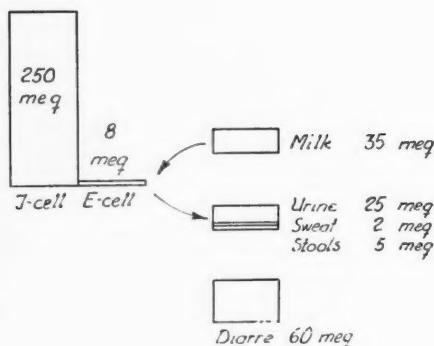


Fig. 5.

Na-Pool
Infant 6 kg

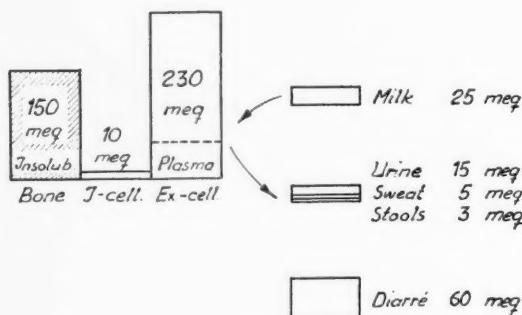


Fig. 6.

The daily sodium turnover (Fig. 5) is $1/10$ of the extracellular amount and the daily potassium turnover (Fig. 6) is 4 times the extracellular potassium.

To summarize: sodium and chloride are mainly extracellular, and their most important function is their osmotic activity.

Potassium is intracellular, depletion may cause weakness increasing to respiratory paralysis and hyperpotassium-emia will induce cardiac disorders, increasing to cardiac arrest.

Some Aspects of Dehydration and its Treatment in Childhood

by NIILU HALLMAN, Finland

Dehydration of the organism may occur when the organism receives insufficient water to satisfy its mineral and fluid metabolism or when the loss of fluid is greater than normal for some reason or another. The latter case especially involves many factors of internal metabolism. Often the loss of fluid and minerals increases because measures are not taken early enough to prevent the loss and because of neglect of the administration of sufficient fluid. This is of significance especially as far as children are concerned as their metabolism as a whole is very rapid.

Depending on how the dehydration originates, the changes in the organism differ. In slow dehydration plasma fluid, extracellular spaces and cells themselves are lost in approximately the same ratio. In rapid dehydration the loss affects first and foremost the plasma and the extracellular space. In haemorrhages blood loss is compensated in the first place from the interstices. In burns and other local tissue lesions the cell fluid and also the plasma fluid penetrate the swelling interstices. Internal metabolic disturbances may also change the relationship between different fluids and cause dehydration in some way or another.

The beginnings of dehydration even cause the secretion of antidiuretic hormone and ACTH from the hypophysis. This results in a maximal reabsorption of NaCl in tubules, an increase in the salt content of the extracellular space and the outflow of fluid from the cells themselves. Depending on the nature of the dehydration, more water also may accumulate in the cells initially; in a later phase the cells always lose water.

In fairly rapid dehydration shock plays an important part and many phenomena can be explained by means of Selye's general adaptation syndrome, in which case the adrenal is a central organ. Planning of treatment must take into consideration the danger of straining the organism excessively and its possible side-effects.

Haematocrit gives some idea of the water deficit in blood. The assessment must also take a potential previous anaemia into account. Plasma proteins give some kind of picture of the state of the capillaries. In a state of rapid dehydration the proteins rise if the capillaries are normal. The best conception of the loss of extra- and intracellular fluid is given by the clinical picture.

Depending on the manner in which dehydration originates, we speak of either a respiratory or a metabolic state. The alkali reserve alone cannot decide which condition is involved; a pH determination is required. In

simple conditions, however, we must be content with the alkali reserve, but in this case it is advisable to remember specifically the original mechanism of dehydration. Children often lose plenty of water under different conditions through insensible perspiration, which complicates the fluid balance and relatively often causes hypermineralisation. The respiratory and metabolic components of the origin of dehydration are then interlinked.

Plasma minerals give a clue to the extracellular fluid also. Chlorides are usually determined in addition to the alkali reserve, giving a clue to potential hypermineralisation. Accumulated organic acids, which occur in children also in other conditions than diabetic coma, make this assessment more difficult.

In simple conditions cation determination is difficult at present although we now have rapid micromethods. The most important of the cations in the clinical sense is potassium, the variation range of which in plasma is relatively narrow. Both an increase and a decrease in plasma cause disturbances first and foremost in cardiac function. These can be detected by an examination of electrocardiographic changes. However, it will be well to remember that the changes may be similar in both hypo- and hyperkalaemia. Nor does the plasma potassium give any idea of the deficiency of potassium and it is possible that the cell deficiency may for its part affect the electrocardiogram despite the fact that the plasma values are normal. Potassium loss in cells occurs more easily in alkalosis, as has been proved by balance tests and investigations of red blood cells and by samples taken from muscle tissue. However, in acidosis too, depletion of potassium occurs and must be considered in the treatment. Kidneys play an important central role in potassium metabolism. As regards other cations a shortage of calcium may also induce symptoms in alkalosis as well as in post-acidotic conditions. Magnesium also shows changes the meaning of which, however, is unknown so far.

Circulatory disturbances and oxygen deficiency are rather significant factors in rapid dehydration, especially when the function of oxygen-sensitive organs such as the brain suffers. Increased blood sugar and the accumulation of organic substances indicate disturbances in the enzyme function of the cells. An endeavour has been made to treat such conditions with cocarboxylase for instance. In infancy especially there are often conditions, such as those caused by serious gastroenteritis, in which toxic factors have been thought, especially earlier, to have a primary effect. True, it is often difficult to distinguish between cause and effect. The accumulation of histamine in the blood established under these conditions may equally well be the result of disturbances in cellular activity due to dehydration. A very important consideration from the treatment point

of view is the effect of dehydration on the kidney and its function, the kidney being one of the most important organs regulating the fluid and mineral equilibrium of the organism. Disturbance of renal function may primarily lead to chronic dehydration conditions such as renal acidosis.

The rapid metabolism of children and especially young children and the associated large daily fluid requirement are conducive to the frequent occurrence of serious dehydration conditions in young children in particular. A contributing factor is the large extracellular space. The regulation of the neuro-hormonal fluid metabolism is more easily balanced in infancy. Psychic factors are also of importance in treatment; in preventive treatment even they constitute a problem for the sufficient administration of fluid.

Severe gastroenteritis with acidosis and various intestinal obstructions with alkalosis are typical in infancy. Diabetic comas and the so-called acetonemic vomiting cause anxiety later. Fluid therapy must, however, be taken into consideration in very many other conditions. It is especially significant in operative activity. The first days of life with their peculiarities must be considered here and also preoperative care in the many conditions of infancy calling for operative treatment. These conditions may be preceded by dehydration originating within a longer or shorter period.

The treatment of dehydration in children often causes difficulties of technical detail. For this reason alone an endeavour must always be made to give oral treatment if possible. If this is impossible, intravenous and subcutaneous administration must be commenced at the earliest possible moment. In this case we are assisted by the superficial blood vessels of the head which despite their small size are well fixed to their base. Hyaluronidase helps the rapid spread of fluid in the tissues. If oral administration is unsuccessful the intravenous drop is the method of choice.

One of the most important tasks in sudden fluid losses is the speedy filling of blood vessels with some large-molecular fluid. With improving circulation the cells themselves work to restore conditions to normal in every respect.

In addition to glucose, sodium chloride and possibly alkali, modern fluid therapy includes also potassium. When dehydration occurs therapy must be given when needed, even intravenously; in this case naturally by the intravenous drop.

In addition to minerals and fluid, care must be taken specifically to ensure the vitamin needs of the organism and to satisfy its energy requirement, for which amino acids and perhaps soon also fat emulsions may be administered in addition to glucose.

The Renal Excretion of Water and Electrolytes in Infants

by J. VESTERDAL, Denmark

In experiments carried out in collaboration with Dr. H. L. BARNETT, New York, premature infants and adults were given water loads of 520–690 ml per sq.m. The minimal osmotic concentration obtained in the urine was about 50 mosm/liter in both infants and adults, but the maximal diuresis of the infants was only 50–60 per cent of that obtained in the adults. This is at least partly accounted for by the considerably lower glomerular filtration rate in the infants.

The maximal osmotic concentration obtainable in the urine is considerably lower in infants. This is only to some extent accounted for by a somewhat smaller response of the infants to antidiuretic hormone. The clinical applications of these findings are discussed.

Circulatory Disorders in Acute Dehydration

by LEENA TUUTERI, Finland

The circulatory disorders in infants suffering from pyloric stenosis and severe acute gastroenteritis with dehydration were studied at the Children's Clinic in Helsinki, using the fluorescein method for determination of the blood circulation time. In infants with pyloric stenosis circulation times at the upper limit of the normal were measured. In infants with severe gastroenteritis a distinct prolongation of the circulation time was found, in many cases to values manifold the normal. In the severest cases a lowered oxygen saturation of the sinus blood was simultaneously noticed. During intravenous fluid therapy a rapid shortening of the circulation time occurred, in the most severe cases normal values were however not found until several days after the beginning of therapy.

On Adrenocortical Hormones in Various Diseases Causing Dehydration in Infants

by HILKKA TÄHKÄ, Finland

A study was made on the effect of desoxycorticosterone acetate (DCA) in 10 infants. They received Doca (Organon) 5–20 mg daily during 5 to 10 days. A rapid gain in weight could be observed in all infants. The children who had been on their ordinary diet during the experiment, showed a

clear decrease in the red cell potassium. This seemed to return to normal in a few days in spite of the Doca medication. A new decrease was, however, to be seen if the dose of Doca was increased. These changes were not observed if the infants had received their ordinary food and a supply of potassium. According to these experiments it seems that it is not advisable to give DCA to dehydrated infants who are suffering from severe infantile diarrhea or pyloric stenosis, which themselves cause a lack of potassium.

An autopsy material of about 70 infants, who had died from severe infantile diarrhea, revealed rather often signs of a possible adrenocortical insufficiency, especially if the children had been ill for a long time before death. To clarify this matter the eosinophilic test of Thorn was performed several times on 32 infants suffering from severe infantile diarrhea. The results showed that the reaction was often abnormal at the beginning of the illness and returned to normal in a few days if the child was improving.

In severe septic conditions in infants DCA and cortisone were used together with antibiotic and fluid treatment during the first day in hospital. So far the results seem favourable.

The significance of DCA, cortisone and salt in the treatment of infants with adrenogenital syndrome and signs of adrenal insufficiency is pointed out.

Indications for Fluid Therapy in Connection with Surgical Manipulations in Infants

by M. SULAMAA and H. TALLQVIST, Finland

Indications for fluid therapy in connection with surgical manipulations in infants can be divided in three main groups: Shock and severe anemia (burns, larger operations, profuse hemorrhages), illnesses in which fluid intake has become difficult (atresias, stenoses, ileus and peritonitis), and illnesses which cause disturbances in fluid balance (dehydration, disturbances in acid-base balance, hypoproteinemia, potassium deficiency). In giving fluid treatment to the newborn and other infants, the danger of fluid retention must be kept in mind. Great care must be taken with NaCl administration. Too much fluid is more dangerous than a relative deficiency. In addition to laboratory data clinical symptoms must be carefully followed. It is better not to try to correct too rigorously the preoperative alkalosis of patients with hypertrophic pyloric stenosis. Utmost care must be given to the fluid therapy of patients with disturbances in the kidney function. Because of the inadequate carbohydrate deposit and the great demand for calories, acetonemia easily develops after a short fast,

and therefore it is not reasonable to let an infant be without food before an operation longer than is necessary. High non-protein nitrogen values can be seen in infants also without a real kidney damage due to dehydration and hemoconcentration. The danger of edema can exist in dehydrated infants despite normal or even increased protein values. In severe cases of hypertrophic pyloric stenoses a potassium deficiency will develop and therefore a preoperative administration of potassium can be of value. After large operations and shock there will often be seen—due to the hyperfunction of adrenal cortex—a potassium deficiency, decrease of eosinophil cells and an increased amount of potassium and corticoids in the urine. The administration of potassium will change conditions towards normal. The parenteral fluid treatment which is given intravenously in the form of a continuous drop is the most important procedure. In less severe cases infusions into a superficial vein of the head are to be preferred to intraosseal infusions because they are quite easy to perform and rarely cause any complications. Only in exceptional cases must the fluid be given subcutaneously. Continuous drop into the rectum may in some cases be of value.

Discussion

Y. Åkerrén, Sweden.—Intensive hunger acidosis with shock was observed in a child about $1\frac{1}{2}$ years old whose acidosis proved to be very resistant to ordinary treatment. In the course of 8-9 hours there was given an intravenous drop infusion of 220 ml of an 8 % NaHCO_3 solution (about 17.6 g NaHCO_3). The CO_2 figure from the outset was 3 m equiv., rising only slowly and reaching 8 m equiv. after 9 hours. After about 17 hours it was 24 m equiv.

B. Vahlquist, Sweden.—When gastric lavage is carried out in cases of poisoning, a fluid surfeit may be provoked and hypo-electrolytaemia may have serious and even fatal consequences if water is used for the lavage. A characteristic feature of such a fluid surfeit thus induced is often haemolysis which probably depends on the severe fall of the osmotic pressure in the blood when fluid passes through the gastric mucosa. Gastric lavage should be carried out with saline solution, not with pure water.

N. Hallman, Finland.—I would like to say that we have made the same observations with regard to the connection between plasma potassium and ECG-changes. Similar changes may be found with high as well as low plasma potassium. The determination of the plasma potassium tells us, however, nothing with regard to the shortage of potassium in the cells of the organism.

SESSION III

Round Table Conference

The Possibilities of Diagnosing Congenital Heart Disease by Physical Symptoms and Signs

E. MANNHEIMER, Sweden, CHAIRMAN, I. BOESEN, Denmark, L.-E. CARLGREN, Sweden,
O. HUSOM, Norway, G. EKSTRÖM and T. MÖLLER, Sweden,
B. JONSSON, Sweden, B. LANDTMAN, Finland.

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E. Mannheimer: Phonocardiography of Congenital Heart Disease.

Auscultation is the most common physical method for the investigation of congenital heart disease in childhood. It is a subjective method of examination. Phonocardiography—registration of the heart's sounds—not only yields objective data concerning the sounds and murmurs heard with the stethoscope, but also other valuable information, which is particularly important with regard to the examination of children with tachycardia.

The following are, in brief, the experiences we have had with our method, calibrated phonocardiography, which has been in use since 1939.

1. In patent ductus arteriosus the typical cases, which constitute about 90 per cent of our material, have a continuous murmur which is loudest over the pulmonary artery. This murmur begins in the middle of systole, reaches its maximum about the second heart sound and dies away far into diastole.

2. In cases of auricular septal defect there is a systolic murmur at the beginning of systole corresponding to the increased minute volume through the narrow infundibular passage of the right ventricle. In most cases the second heart sound is not accentuated, but widely split, and this corresponds to the right bundle-branch block.

3. The systolic murmur associated with ventricular septal defect is less typical and is followed by a second pulmonary sound which is often accentuated.

4. The harsh systolic murmur of valvular pulmonic stenosis is of great amplitude. It begins somewhat after the first sound. The second sound is "pure", because the pulmonary artery component is often lacking. The systolic murmur of infundibular stenosis begins directly after the first heart sound. The pulmonic component of the second sound is delayed and often weak in cases with a large "third ventricle".

5. The systolic murmur of aortic stenosis is loudest over the aortic root. As Leatham has already shown, it is diamond shaped and is placed in the middle of systole.

The phonocardiograms described here are of essential value in isolated cases. With a combination of lesions, the findings of auscultation and phonocardiography are often complicated and difficult to interpret.

Ib Boesen: Defects of the Ventricular and Auricular Septa.

In distinguishing between the various congenital diseases of the heart, dyspnoea, malnutrition, frailty, pallor and lassitude are so non-specific as indicators of insufficiency that they have little value for the differential diagnosis. On the other hand, they are most useful in framing a prognosis and are thus most decisive when making the choice of the eventual treatment.

“Voussure”, “fremissement” and the delimitation of the heart’s boundaries by percussion are of no diagnostic value.

Cyanosis forms the basis for a practically applicable and clinically useful classification of the congenital diseases of the heart, with or without right shunt, left shunt, although it is only when the shunt is so great that the arterial oxygen saturation is under 80–85 per cent that we can sort out our cases in this way.

The other methods of examination depending on physical means for diagnosis are auscultation, electrocardiography, measurement of the blood pressure in arms and legs, and an ordinary radiological examination including screening. With regard to the congenital diseases of the heart not associated with cyanosis, the value of such an examination consists especially in that, without any further examination, we can with great certainty distinguish between the three operable types — patent ductus arteriosus, coarctatio aortae, and isolated stenosis of the pulmonary artery, at any rate in children more than 3 to 4 years old.

Patients suffering from defects of the auricular or ventricular septa often present characteristic combinations of stethoscopic, electrocardiographic and radiological findings. We may, however, overlook one of the already mentioned, operable types presenting the features which are usually described as typical of a septum defect. We cannot, however, be quite categorical with regard to the unreliability of the diagnosis by physical means in these cases. It is generally only in the severe and moderately severe cases that the diagnoses are confirmed, as the slight cases rarely are examined by catheterisation of the heart and/or angiocardiography, and confirmation of the diagnosis by a post-mortem examination is usually lacking. We can therefore not rest satisfied with the physical diagnosis when the manifestations of a septum defect render the child so ill that treatment is necessary. Under these circumstances catheterisation and/or angiocardiography must be undertaken so as to make sure that we have not overlooked one of the types suitable for operative treatment, when the heart disease is so troublesome that it entails signs of insufficiency calling for treatment.

When children are less than 2 to 3 years of age, and particularly in infancy, the diagnosis by physical means of a congenital heart disease with left-right shunt is rarely so reliable that we can be sure of the character of the affection with which we are dealing.

Lars-Erik Carlgren: Pulmonary Stenosis without Overriding Aorta.

A correct bed-side diagnosis is most often possible in this cardiac malformation. This is specially true in simple valvular stenosis. Severe cases are characterized by dyspnoea on effort, peripheral cyanosis, loud systolic murmur and thrill in the pulmonary area, single second heart sound—which is not necessarily weak—right ventricular heave, and presystolic pulsation of the jugular veins. In addition, the ECG shows right ventricular hypertrophy of often extreme degree and X-ray reveals pulmonary ischemia, post-stenotic dilatation of the pulmonary artery and right ventricular enlargement. Mild cases, on the other hand, are as a rule symptom-free and there is little to be found except a pulmonic systolic murmur and thrill; the second sound is often split. ECG is normal and a post-stenotic dilatation is the only pathological finding in the X-ray. In moderate cases the symptoms and signs have an intermediate position.

Simple infundibular stenosis is much less common and does not differ from valvular stenosis functionally or symptomatically except that the murmur and thrill are situated at a lower level. There is no post-stenotic dilatation of the pulmonary artery in infundibular stenosis.

Pulmonary stenosis without overriding aorta may be combined with a left-to-right shunt through an atrial or ventricular septal defect. This renders diagnosis more difficult. In some cases the shunt symptoms may overshadow those of the stenosis while in others the outstanding symptoms may be stenotic and the shunt is overlooked.

If pulmonary stenosis is severe enough and there is a septal defect, especially of the atrial wall, or even a patent foramen ovale, the shunt may be reversed. Cyanosis of central origin then appears and the condition may be clinically indistinguishable from the tetralogy of Fallot. In such cases a correct diagnosis is necessary since the Blalock-Taussig operation is contra-indicated in pulmonary stenosis without overriding aorta.

Odd Husom: Tetralogy of Fallot (1). Pseudo-Truncus (2). Tricuspid Atresia (3). Transposition (4). Eisenmenger's Complex (5).

A brief account of the haemodynamic conditions: Pulmonary oligaemia and hypotension predominate in types 1, 2 and 3 and pleonaemia and/or hypertension in types 4 and 5.

In none of these five types of heart disease are there any pathognomonic anamnestic or physical signs of value. The following characteristics are of more or less relative value. *The patient's age:* Types 2, 3 and 4 recede into the background after the age of 2 years, as the mean duration of life is shorter. The heart disease is more serious than in types 1 and 5, physical development is more retarded, and functional capacity is more limited, the patients seldom being able to walk more than a few meters. Attacks of asphyxia and squatting occur in the majority of types 1, 2 and 3, in the minority of types 4 and 5. Coughing is common in type 4, and haemoptysis occurs now and then in type 5. Angina is indicative of types 4 or 5, but is rare. The symptom common to the group is cyanosis of a central type dating nearly always from the neonatal period in types 2, 3 and 4, being rare after the age of 2 years in type 1, and usually occurring later in type 5. It may be more marked in the upper than in the lower half of the body in cases of transposition with a persistent ductus arteriosus. This is the only pathognomonic symptom in the group taken as a whole, but it is difficult to evaluate and is therefore of doubtful value. Clubbing and polyglobulia are of the same degree at the same age, and shunt of the same size. Dilatation of the veins on the dorsal skin of the fingers is said to be common in cases of transposition. Presystolic venous pulsation in the neck, and presystolic pulsation of an enlarged liver are sometimes distinct in type 3, being rare in the other types.

Among the physical signs concerning the heart, a visible and palpable pulsation in the second left intercostal space should be emphasized as being indicative of hypertension of the pulmonary artery, pointing perhaps to type 5 in particular. This condition is never present in cases of hypotension of the pulmonary artery. Splitting of the second heart sound over the origin of the pulmonary artery is a very valuable sign as it excludes types 1, 2 and 3 and points to types 4 and 5. Also suggestive of types 4 or 5 is a diastolic decrescendo murmur, often very weak, over the origin of the pulmonary artery. A continuous murmur over the thorax, particularly the interscapular space, is suggestive of abnormal bronchial arteries and pseudotruncus. The loudness of the second heart sound over the origin of the pulmonary artery and a systolic murmur are of little diagnostic value.

We never get further than a probable diagnosis, but we can often succeed in distinguishing between heart disease with hypertension of the pulmonary artery and with hypotension.

Special methods of examination are always necessary for a specific diagnosis. An electrocardiogram is useful only when it shows left axis deviation which is typical of type 3, but is not pathognomonic of it. The X-ray examinations usually distinguish between hypertension and hypotension

of the pulmonary artery, and often provide characteristic pictures of the different types, particularly type 1. Catheterisation of the heart may confirm the opinion arrived at regarding the pressure in the pulmonary artery, but has only limited possibilities with regard to types 2, 3 and 4. The special importance of angiocardiology for a more detailed topographic diagnosis of morbus coeruleus is emphasized.

G. Ekström and T. Möller: Diagnosis by Physical Means of a Persistent Ductus Arteriosus.

As a rule, the diagnosis of a persistent ductus arteriosus is quite easy. It is based on the continuous murmur heard over the 2d left interspace. In more than 90 per cent of all ducti there is a continuous murmur, which in our material was absent in only a small group (about 6 per cent of the total). Accordingly, we distinguish between typical and atypical cases. The behaviour of the murmur, confirmed by phonocardiographic examination, is the subject of a very careful study. An atypical murmur may be due to hypertension of the pulmonary artery and faulty compensation of the heart. It is probable that an atypical murmur may occur also quite early in infancy before the development of the normal difference in pressure between the systemic and the pulmonary circulation. There is nearly always a pause between the first heart sound and the beginning of the continuous murmur which, in all typical cases, reaches its maximum intensity about the second heart sound. The surgeon can in every case demonstrate "fremissement", at least when he palpates the exposed pulmonary artery. If the "fremissement" is strong enough, it can even be felt outside the thorax over the 2d left interspace.

It is not correct, as maintained earlier, that the second heart sound is always accentuated. An account is given of the number of cases with an accentuated P_2 in our material.

The heart is evidently enlarged when the shunt is great. "Voussure" develops when an infant is affected by heart enlargement. The number of cases of "voussure" is being reviewed, and other conditions, determined by the degree of the shunt, are discussed.

It has often been maintained that a persistent ductus arteriosus inhibits the physical development. On the whole, the measurements of length and weight fall within the permissible variation limits. Neither can we record any noteworthy improvement of physical development on post-operative follow-up examination. On the other hand, when the ductus is very wide, the physical development is inhibited.

In our material of persistent ductus arteriosus, girls outnumber boys more than in earlier publications, well over three-quarters being girls.

Bengt Jonsson: Anomalies of the Blood Vessels. Subaorta- and Aorta-Stenosis. Coarctatio Aortae.

The most important physical sign indicative of coarctatio aortae (isthmus-aorta-stenosis) is an increase of the blood pressure in the upper half of the body and a blood pressure which is low and may not be audible by auscultation over the lower extremities. In childhood, absence of femoral pulsation in the groin is practically a pathognomonic sign of this disease. Palpation of the arteries in the groins should therefore form part of every routine examination of the cardiovascular system. Stenosis proximal to the origin of the left subclavian artery will produce absence of pulsation in the left radial artery.

Now and then hypertrophy of the left ventricle may be revealed by a hyperdynamic apex beat far over to the left. The maximum intensity of the systolic murmur is usually over the aorta, and it is easily audible behind, over the dilated intercostal arteries. This malformation usually occurs isolated, but it is not rare to find it associated with mitral stenosis and a patent ductus. The diagnosis of coarctatio should therefore be easy. A selective angiographic or a thoracic aortographic examination should be insisted on before an operation in order to find out if the stenosis is operable or not, and to inform the surgeon before he operates of the anatomical conditions which vary greatly from case to case.

The infantile type of coarctatio aortae is characterized by stenosis of the ascending aorta or arcus. The head and arms are supplied with blood from the left ventricle, and the lower half of the body by the pulmonary artery which, through a wide ductus arteriosus, connects directly to the descending aorta. In such rare cases one should find more marked cyanosis in the lower than in the upper half of the body. The problem is difficult as the blood becomes mixed through the defect of the septum always to be found in this syndrome. There is no continuous or other typical murmur.

Duplication of the arch of the aorta sometimes gives rise to stridor and/or dysphagia. Although very rare, the same condition may be caused by a subclavian artery, curving out from the descending aorta behind the trachea.

In cases of congenital valvular and subvalvular aortic stenosis in childhood, the murmur presents the features typical of stenosis of the aorta as described by Leatham. It is placed in the middle of systole and has a rhomboid shape in a phonocardiogram, its maximum being always over the origin of the aorta. "Fremissement" can be detected on palpation, and in typical cases can be followed up along the main branch of the right carotid. The second heart sound is weak. The aortic component may possibly be completely absent in valvular stenosis.

B. Landman: Postoperative Changes in the Electrocardiogram in Congenital Heart Disease.

Electrocardiograms of 46 cases of pure pulmonary stenosis, of 41 cases of coarctatio of the aorta and of 73 cases of patent ductus arteriosus were studied before and after surgical correction of the defect. The majority of the patients were children and the postoperative observation period varied between 3 months and 5 years. In each case, 60 electrocardiographic particulars were analyzed before and after the operation.

In each group, the electrocardiograms taken at the last postoperative examination revealed significant changes as compared to the preoperative tracings.

The changes in the electrocardiogram which occurred after valvulotomy for pure pulmonary stenosis were considered due to the diminished load on the right side of the heart. There was a positive correlation between the degree of the electrocardiographic changes and the pressure in the right ventricle.

The changes in the electrocardiogram which were registered after surgical repair of the coarctation were interpreted as signs of a diminished left ventricular stress. A positive correlation was found between the postoperative changes in the electrocardiogram and the fall of the systemic blood pressure.

Sixty-five of the patients with patent ductus arteriosus presented a typical continuous murmur and electrocardiographic signs of left ventricular preponderance. Eight patients showed electrocardiographic evidence of right ventricular or combined ventricular stress. In these cases cardiac catheterization revealed an increased pressure in the pulmonary artery. Following ligation of the ductus the electrocardiographic signs of heart strain disappeared in the majority of cases. A positive correlation was found between the size of the ductus and the changes in the electrocardiogram.

Evidence is present that electrocardiography offers a simple and valuable means for the determination of differential heart strain and, consequently, for the evaluation of the benefits derived from surgical corrections of cardiac malformation.

Discussion

Patent Ductus Arteriosus

Lars-Erik Carlgren, Sweden.—I would like to mention the significance of the increased pulse pressure due to lowering of the diastolic blood pressure. It manifests itself as a so-called Corrigan pulse often found in cases

of a patent duct and best felt over the femoral arteries. The diagnostic value of this phenomenon is great, particularly in atypical cases with a pure systolic murmur.

B. Jonsson, Sweden.—In addition to a systolic murmur, an accentuated P_2 , and great amplitude of the pulse, we must also insist on considerable enlargement of the heart before suspecting an atypical ductus arteriosus. When an infant shows no appreciable enlargement of the heart, it is thus safe to defer a special examination without risking the overlooking of a ductus arteriosus.

Ib Boesen, Denmark.—I would like to ask Mannheimer whether in most cases of a persistent ductus arteriosus in infancy we may expect a systolic murmur, i.e. one without a diastolic component, as commonly assumed.

E. Mannheimer, Sweden.—No, most of the infants show a continuous murmur, but there are exceptions.

Aorta Stenosis. Coarctatio Aortae

Ib Boesen, Denmark.—With regard to the diagnosis of coarctatio aortae I would like to endorse the point emphasized by Jonsson—that palpation of the femoral arteries in the groins should form part of the routine of ordinary physical examinations of children. In this way we would find one case among every 3,000 children examined.

B. Landtman, Finland.—In infancy it is often difficult by palpation to decide if the pulsation of the femoral arteries is weak. At this age it is also difficult to measure the blood pressure in the usual way, and it may often be helpful to employ the so-called "Flush technique" for the determination of the blood pressure. The measurement is effected in the following way: A rubber glove is knotted tight round one of the patient's hands, inducing an ischemia which can be seen best in the palm of the hand. A blood pressure cuff is now applied to the upper arm, and the column of mercury is pumped up to a level of 200 mm. The rubber glove is now removed, and the column of mercury is allowed to fall slowly. Its level is recorded at the moment when the ischemic skin of the palm of the hand turns red. This reading gives the systolic pressure.

T. Möller, Sweden.—At the Crown Princess Louise's Hospital in Stockholm we have come to the conclusion that it is very difficult to distinguish in infancy between the various forms of localized cyanosis of the lower half of the body in cases of coarctatio aortae with persistent ductus arteriosus.

and other disorders of the circulation with right-to-left shunt. In this respect we differ from the teaching of standard text-books.

B. Jonsson, Sweden.—Our material from the Karolinska Hospital in Stockholm does not include any case of heart decompensation in infancy, whereas Gross, among others, has found several such cases. On the other hand, our radiologists have shown that enlargement of the left auricle may exist in small children, but when such cases are followed this enlargement recedes as the child grows older. In several such cases it has been possible by clinical means to demonstrate signs of decompensation involving the pulmonary circulation. It is possibly the collaterals taking over and relieving the left chambers.

Pulmonary Artery Stenosis without Overriding Aorta

B. Jonsson, Sweden.—It is often possible by physical examination to distinguish between valvular and infundibular stenosis of the pulmonary artery. In the latter, one can often detect a definite pause between the murmur and the second heart sound. When the third ventricle is large, it takes a considerable time to empty, and by measurements of the pressure we have succeeded in showing that the infundibulum contracts later than the other chambers. The murmur develops only during the passage of the blood through the infundibular stenosis, but not during the emptying of the third ventricle. The closure of the pulmonary valve gives rise to a normal second heart sound, but it comes remarkably late.

Septum Defects

E. Mannheimer, Sweden.—Boesen takes too pessimistic a view of the matter. It is possible to distinguish between a defect of the auricular and of the ventricular septum. I want to remind you of what was said in my phonocardiographic survey.

B. Jonsson, Sweden.—It is possible by means of palpation to form an estimate of the hypertrophy of the right and left ventricles. Hypertrophy of the left ventricle leads to lateral displacement of the apex beat which is wider in extent and duration, whereas hypertrophy of the right ventricle does not give rise to a palpable apex beat, but to a parasternal lift. In cases of defects of the auricular septum, it is only the right ventricle which is dilated and hypertrophied. On the other hand, defects of the ventricular septum give rise to hypertrophy of the left ventricle and also of the right chamber when the defects are serious. It is therefore possible by means of a physical examination to distinguish with consider-

able certainty between defects of the auricular septum and the ventricular septum. The murmurs and other factors are also different in the two conditions as already shown by Mannheimer.

Odd Husom, Norway.—When defects are great, auscultation may reveal a phenomenon worth noting—a diastolic rumbling murmur reminiscent of mitral stenosis.

Electrocardiographic Examinations

T. Möller, Sweden.—At the Crown Princess Louise's Children's Hospital in Stockholm I have collaborated with G. Ekström in a follow-up examination of 255 patients operated for ductus arteriosus with special reference to electrocardiographic changes before and after the operation. In 52 cases the observation period was 5–10 years. The shortest observation period was half a year. The electrocardiographic findings before and after the operation were compared according to whether the duct was narrow, wide or atypical. When it was narrow, the electrocardiogram was practically normal after the operation, and when the duct was wide the electrocardiogram, which had been normal in 49 per cent of the cases before the operation, became so only in 63 per cent after the operation. In cases of an atypical ductus, the electrocardiogram was never normal either before or after the operation. Pathological electrocardiograms before and after the operation were compared with reference to affections of the myocardium, hypertrophy, and the position of the electrical axis.

General Discussion

B. Vahlquist, Sweden.—The discussion has dealt with the possibilities for a specific diagnosis of different kinds of heart disease when only simple tests for a physical examination are employed. This is assuredly a matter of importance to the work of a heart laboratory whose capacity would be increased, and several patients would be spared a relatively comprehensive examination, if such simple methods could be relied upon. But for the practising pediatrician there is another aspect of the problem. He has to answer two simple questions: Is this a case of heart disease, and if so, is it operable or not? It would be interesting to learn the opinions of others on this matter.

E. Mannheimer, Sweden.—It should not be necessary to admit all patients to hospital, an out-patient examination is often sufficient, at least to decide if and when the patient ought to be hospitalized.

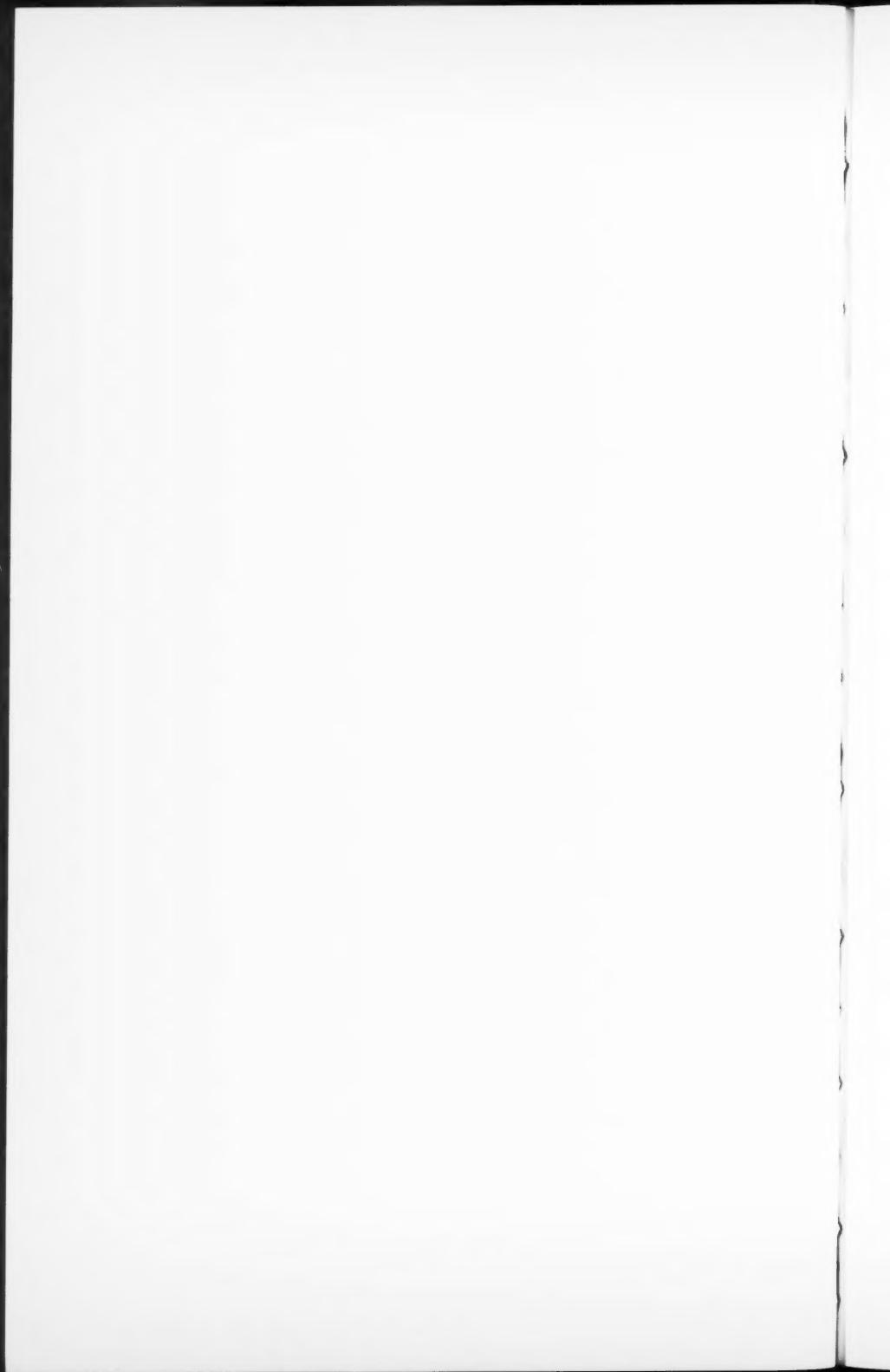
B. Landtman, Finland.—Experience has shown that special hospital departments are necessary for cardiology in childhood. The examination

of such cases requires long, special training and considerable personal experience on the part of the doctor. He also needs costly apparatus which is not available in an ordinary pediatric hospital. Every pediatrician working outside the sphere of a special heart hospital has a great task to fulfill, particularly when he has to sort out the cases in need of a special examination. With regard to congenital heart disease in childhood it is of prime importance to choose the suitable time for such an examination. Operation of infants should be undertaken only on vital indications.

B. Jonsson, Sweden.—The pediatrician without training in this specialty does not see so many cases that he acquires the experience necessary for diagnosing with accuracy and distinguishing between various affections by means of physical tests. If, however, in the course of his training he can serve for half a year in a special hospital and see several hundred cases of heart disease, I believe that he would have a great chance to treat many cases single-handedly. In this connection it is essential that he can invoke the aid of a radiologist with experience in this field.

K. Kaijser, Sweden.—It is reassuring to hear that Mannheimer continues to attach so much importance to careful auscultation with the stethoscope in spite of the more modern aids to the diagnosis of heart disease now available. This matter gives me the opportunity to ask the following question: Is it a useful diagnostic device to auscultate a patient in different positions, or is it no longer necessary to pay attention to variations in the character of a murmur in different positions of the body? We all know that a murmur often diminishes when the patient sits up, becoming louder when he assumes the horizontal position. In order to hear more clearly a weak murmur I auscultate the heart in certain cases with the patient placed in a bed with the foot end raised and the head end lowered. In this way a weak or doubtful murmur becomes much plainer in many cases. By changing the position of the patient a quantitative change in the character of a murmur can be heard, and this may be helpful when it is faintly audible. On the other hand, it is doubtful if the changes in the character of a murmur evoked by varying the patient's position can be of any assistance to the diagnosis of different types of heart disease. I should be glad to have an answer to this question.

E. Mannheimer, Sweden.—I would like to sound a note of warning against a too elaborate refinement of the physical diagnosis. We must not attach too much importance to faint systolic murmurs. As seen from this conference there are many other and definite symptoms and signs that can lead us towards a correct diagnosis.



SESSION IV

Free Subjects

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A Follow-up Study of Children born of Mothers suffering from Toxaemia of Pregnancy

by MARJATTA KUNNAS, Finland

The material consists of 288 children, 53 examined by the author, 127 cases studied by questionnaires. The mortality was 26.1 per cent. The perinatal mortality was 6 times higher than in the control series.

The somatic and mental development of these children did not differ from the normal.

Discussion

T. Salmi, Finland.—About 20 years ago I noticed that the infants of mothers suffering from nephrogestosis had an increased blood pressure and non-protein nitrogen. A couple of weeks after birth both these conditions were normal, as was the later general development of these children.

Icterus Neonatorum Prolongatus Indicating an Early Diagnosis of Congenital Myxoedema

by YNGVE ÅKERRÉN, Sweden

On the basis of a number of cases, one of which will be given a short report, the author points out the not unusual coincidence between icterus neonatorum prolongatus of a remarkable duration, but otherwise of a physiologic type, and congenital myxoedema. Both conditions are singularly unusual. This connection, which previously was disregarded, is of practical importance from the differential diagnostic point of view. The knowledge of this syndrome should facilitate the early diagnosis of congenital myxoedema, which is important, *inter alia*, from the therapeutic point of view. An accurate check-up until the diagnosis, congenital myxoedema, can be made or excluded, is therefore necessary in icterus neonatorum prolongatus, especially when there is a remarkable duration of this condition. Myxoedema is thus a diagnostic possibility not yet observed, when making the differential diagnosis of icterus neonatorum prolongatus.

Discussion

R. Amlie, Norway.—A case of icterus neonatorum prolongatus with an unusual course has recently been treated in the Children's Hospital. The jaundice started on the 5th–6th day after birth and increased considerably during the next 6 weeks. At the age of 8 weeks the infant was admitted to the hospital and a hypothyreosis was diagnosed. The jaundice disappeared after $2\frac{1}{2}$ months.

The admissions of hypothyreosis to this department during the last $1\frac{1}{2}$ years were shown in a couple of tables. Altogether 24 new cases had been admitted, of which 6 had suffered from icterus neonatorum prolongatus.

The weight at birth of these infants was on an average high. Excluding 4 cases presumably 3 weeks pre-mature born, the average weight was well over 4 kilogrammes.

K. Palmén, Sweden.—The two cases of congenital myxoedema which I have seen during the last two years have shown another early symptom: Severe distention of the abdomen. Both infants, whose ages were 4–5 weeks, were admitted to hospital as cases of acute abdomen with the symptoms of intestinal obstruction. The first patient had the appearance of a slight myxoedema, was treated with thyroid tablets, the abdominal symptoms disappearing in 2 days. The other case showed no definite signs of myxoedema. The symptoms disappeared quickly on thyroid medication and the further course of the case showed that this patient also had suffered from hypothyreosis.

Grete Gørtz, Denmark.—When Dr. Åkerrén finds that a certain number of myxoedema patients suffers from icterus gravis, I would like to present the problem the other way round: Are there large numbers of cases of icterus gravis showing the percentage frequency of associated myxoedema? Such a percentage is assuredly not very high.

Is it possible by a clinical examination to distinguish between the symptoms to be found (1) among patients suffering from icterus gravis with myxoedema and (2) patients suffering from icterus gravis without myxoedema?

Should icterus be the aetiological factor in myxoedema one might expect to find icterus entailing some cerebral affection or other. We have the condition known as "kernicterus". It is conceivable that a cerebral affection may disturb the vascular supply to the hypophysis. Should this be the case, then a beginning affection of the hypophysis could be demonstrated by the micro-variations in the ACTH-level. Should any of these patients

die, I would suggest that the specimens were to be examined by a neuro-anatomist.

Dicumarol may be given if the vascular affection has a thrombotic character.

The Prognosis of Congenital Hypothyreosis, Judged from a Larger Material

by M. D'AVIGNON, Sweden

A follow-up examination of close to 300 patients treated in various children's hospitals and clinics throughout Sweden under the diagnosis of congenital hypothyreosis, hypothyrodism, myxoedema or cretinism has been undertaken. These follow-up examinations were carried back as far as the medical records gave complete pictures of the cases. Among these patients 99 cases of definite congenital hypothyreosis were found. The criteria for this diagnosis were very strictly defined. The follow-up examination consisted of a supplementation of the anamnesis and an investigation of the social environments. Beside the somatic examination a Termann-Merrill testing was performed. The material was divided in groups: Group III, where the treatment had been inadequate, either very sporadic or instituted too late—or a combination of the two latter conditions. Group I, where the treatment was initiated early, was followed consistently and where the doses given had been high. This leaves an intermediate group, group II, where the treatment had been either relatively late in initiation or early started, but with small doses.

It was then found that the patients belonging to group III had an I.Q. of 48.5 ± 0.9 , group II: 71.5 ± 3.7 , and group I: 92.2 ± 3.2 .

Consequently, the conclusion is drawn that the patients belonging to group I show the best results, and that the treatment given to them therefore must be considered the most advantageous. The treatment will be discussed later, whereby many other problems in this connection will be dealt with.

The Incidence of Diabetes in Children of Young Diabetic Mothers

by JØRN DITZEL, PRISCILLA WHITE and JANINE DUCKERS, Denmark

A survey of a study of 105 children of young diabetic mothers was given.

In these children three striking deviations from the normal were demonstrated. The first was a superiority of growth in stature and weight.

The second was a tendency toward the development of hyperglycemia and glycosuria and the third was an apparently well defined change of the vascular pattern of the smaller vessels as observed in the conjunctiva.

There was found a positive correlation between the degree of vascular changes in the smaller blood vessels and the abnormal glucose tolerance test as well as growth peculiarities according to Wetzel's grid.

It is therefore suggested that the precipitating factor of these abnormalities is the same and that possibly it may be of pituitary origin.

Do Vaccinations Change the Immunisation Stability?

by OLE WASZ-HÖCKERT, Finland

This is a preliminary report on experimental studies of 120 guinea-pigs, which were prepared after TB-inoculation ($H_{37}Rv$) with various vaccines (BCG-, variola-, pertussis-, pertussis-diphtheria-, and triple vaccine). No definite difference was observed between vaccinated and non-vaccinated animals when using stronger inoculation. On the contrary, a dose of 0.1 mg of $H_{37}Rv$ in 50 guinea-pigs gave earlier tuberculin reactions and showed more advanced tuberculosis on autopsy in the vaccinated animals than in the control group.

Discussion

K. Wilken-Jensen, Denmark.—If the guinea-pigs have received the same dose of vaccine as children are given, it is not strange that these animals were unable to combat the infection. The doses would correspond to 30 ml of diphtheria vaccine or 1 ml of BCG-vaccine in a 1 year old child. Such a dose would undoubtedly suppress the immunizing factor with the result that the infection would spread.

B. Vahlquist, Sweden.—I have found the observations made by Dr. Wasz-Höckert interesting, but two points ought to be emphasized: The fact that the animal tests only show that the rate of the spread of infection is increasing, and the fact that the dose of the vaccine employed has been very high. The coincidence of vaccination with disease in human beings may at any rate be a matter of chance, considering the great number of vaccinations now performed.

O. Wasz-Höckert, Finland.—The dose of the injected vaccine was intentionally kept high in order to evoke experimentally the clinically observed phenomenon. The investigations have followed two lines: (1) To note the

factors which diminish the organism's powers of resistance to infections in order to, later on, with a view to clinical profit, to expose if and how the power of resistance can be stimulated and improved. (2) To evolve a quicker guinea-pig test for the diagnosis of tuberculosis. We clinicians must now wait 6 weeks for the guinea-pig test. A reduction of this span of time to, for instance, 3 weeks would be welcome. Furthermore, I would like to stress the point that this is a discussion of research work of the problems of immunity and not an attempt to discredit vaccinations. Obviously we pediatricians ought to examine carefully the children we intend to vaccinate.

V. Rantasalo, Finland.—Whether the vaccinations are done with living virus (variola) or with toxins (diphtheria, etc.) we often find an outbreak of some infection. This phenomenon is not due to chance, but is caused by the same principle which Wasz-Höckert has described.

The Technique of Pneumo-encephalography in Children

by SVEN BRANDT, MAZAR DE LA GARDE and TH. ROSENDAL, Denmark

The indications for pneumo-encephalography in a pediatric department are practically never absolute, but only relative. It may be a valuable supplement to the clinical examination e.g. in cases with mild or questionable neurological signs, but for some other reason suspected of organic cerebral disease of an atrophic nature. In epilepsy and in cerebral palsy pneumo-encephalography may indicate the localization of the pathological process—whether high or low in the central nervous system.

At Queen Louise's Hospital for Children, Copenhagen, pneumo-encephalography is performed as a team work, the anaesthetist taking over all responsibility for the child, allowing the neurologist to concentrate on the examination.

The children are examined in Narcoderm-Pethidin anaesthesia given intravenously (5 % Narcoderm, 5 % Pethidin). This is given in consecutive doses and the patient is steadily kept in the lightest possible anaesthesia. Oxygen is supplied through a hollow tongue depressor. The first picture is taken of a sitting patient after a partial replacement of spinal fluid with air—usually 5–10 ml fluid being exchanged each time. The first portion of air is given before any spinal fluid is removed. A filling of the 4th ventricle with a minimum of air was obtained in 34 of 53 cases by this technique. If no air has reached the ventricular system after the first 10 ml, a change

in the head position or in the position of the cannula should be effected. Complete negative filling by this technique was the result in only three of 53 cases.

We observed only a very slight drop in the blood pressure of our patients when in sitting position (the head suspended in a Glisson suspender). Air insufflation was followed by a slight rise in blood pressure and a fall in pulse rate. After the removal of the cannula the remaining pictures were taken in the usual positions with the patient prone and supine. The technique for the filling of the temporal horns was demonstrated on slides.

The amount of air given varied from 10 to 50 ml.

Only insignificant complications were observed, e.g. headache, vomiting and a slight rise of temperature. They rarely lasted more than one or two days.

The anaesthesia was complicated in two cases by a short cessation of respiration. This was easily treated by the anaesthetist. In one case the cause was over-concentration of Pethidin. In the other case the respiration stopped each time the child was turned to the prone position.

Changes of the Eye Similar to Retrolental Fibroplasia Induced by Exposure of Newborn Mice to Concentrated Oxygen

by L. J. GYLLENSTEN and B. E. HELLSRÖM, Sweden

Newborn full-term mice were subjected to exposure in 98–100 % oxygen (a) intermittently, (b) continuously, or (c) for five days followed by rapid transfer to normal atmosphere. The development of the eyes was observed histologically. Intermittent exposures caused a high frequency of persistence, proliferation and dilatation of the retrolental hyaloid vessels with hemorrhages in the primary vitreous body. Continuous exposure to oxygen caused a persistence and proliferation of the retrolental hyaloid vessels and a retarded formation of retinal vessels. Small intraocular bleedings occurred occasionally. Continuous exposure to oxygen followed by a rapid transfer to, and stay in normal atmosphere caused a dilatation and a progressive proliferation of the retrolental hyaloid vessels and of the retinal vessels with capillary buddings from the retinal vessels into the vitreous body. Hemorrhages from the newly formed vessels were frequently found. The retina showed progressive irregularities, proliferations and foldings. These findings were similar to those found in the early stages of retrolental fibroplasia.

Treatment of Petit Mal with Dimedion, Tridione, Paradione and Milontin

S. BRANDT and S. BILLE, Denmark

Of 35 children only 10 were cured and 10 improved after the first trial with one of the four drugs. Side effects causing the discontinuation of the drug were noticed in four cases. Following experiments with one or more of the other preparations complete control of seizures was observed in 19 cases, improvement in 8. No side effects were found in 3 of the 4 children who had got side effects from the primary medication, when given one of the other drugs.

Serious granulocytopenia after Dimedion (3-ethyl-5,5-dimethyl-oxazolidine-2,4-dione) was experienced in one case.

The pharmacological effect of these four similar chemical substances does not seem to be quite identical. A certain difference in the response of each individual both in relation to the clinical effect and with regard to the side effects is postulated, opening wider aspects for the clinical use of these newer drugs. Should no results be obtained with the one drug, then the treatment ought to be carried on with one of the other similar drugs.

Causal Relations in Accidents to Children

by R. BERFENSTAM, Sweden

The task of preventing accidents should be based on current statistics and an investigation of the probable causes and factors in the individual and his environment. For the past year an investigation has been carried out at the University Hospital in Uppsala. By means of conversations with the mothers of children injured in accidents we have tried to obtain details of how the accident occurred, what the child was doing and its state of mind at the time of the accident. We have, moreover, tried to find out more about the child's manner of reacting and development, as well as details of the conditions in the home, the size of the family and the dwelling, etc.

The investigation included 479 child casualties and 113 control children, all below 10 years of age.

A preliminary scrutiny of the material shows among other things that $\frac{1}{3}$ of the children had already previously been exposed to more serious injuries. It appears that the lowest income group as well as cases from families with several children were proportionately overrepresented. In

the latter category the fact that mothers find it difficult to pay sufficient attention to their older children has undoubtedly some connection with the matter. Nothing has appeared to support the view that previously experienced serious illnesses have any significance as a predisposing factor. In $\frac{1}{3}$ of the cases the parents thought that the accident could have been avoided.

Discussion

B. Vahlquist, Sweden.—Seeing that accidents have reached such a pitch that at certain ages they cause just as many deaths as all the main diseases together, it is obvious that this state of affairs must concern pediatricians considerably. Accidents must be prevented on the same lines as followed in the prevention of disease. Education, propaganda, etc. are our most important weapons. In Sweden the Swedish Red Cross has taken up this task in close co-operation with a group of pediatricians. We must also co-operate with various organisations which are already working with the same aim.

Film showing Cataleptic Seizures of a Hysterical or Simulatory Character in a 7-year-old Epileptic Boy

by SVEN BRANDT, Denmark

This boy had suffered from typical epileptic seizures over 9 months partially controlled by Dilantin and Phenobarbital. After this period he started to have a new type of seizures, of a cataleptic character, lasting for several minutes and accompanied by analgesia. His EEG was abnormal with paroxysmal discharges, but no direct correlation could be found between the cataleptic attacks and the EEG abnormalities. His seizures could be stopped by clasping his stomach. The emotional background might have been a temporary parental rejection caused by moving into a new house. His strange seizures had greatly aroused the interest of his schoolmates and probably supplied him with a special satisfaction at being the centre of their attention.

SESSION V

Neonatal Asphyxia

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Pathological Anatomy of Asphyxia Neonatorum

by E. K. AHVENAINEN, Finland

To begin with it seems necessary to make clear what is meant by asphyxia and anoxia. These words have been used simultaneously, and even as synonyms. Asphyxia and anoxia are, however, not quite identical conceptions. Asphyxia neonatorum is a clinical "diagnosis" of a state when the respiration of the newborn infant is impaired. Anoxia by definition means oxygen deficiency.

Studies on the basis of autopsy material in this field mostly deal with morphological findings. Of course, many of the asphyxiated newborn who die are anoxic as well. Since the degree and duration of anoxia has usually not been determined, it is not possible to compare the severity of morphological findings with the severity of anoxia. Experimental investigations have mostly dealt with anoxia. One has to be careful when drawing any conclusions on the basis of these animal experiments if one is talking about asphyxia of newborn infants.

The pathology of asphyxia of the newborn can be reviewed from two directions: (I) Tissue and organ changes which can be the cause of asphyxia, (II) Tissue and organ changes possibly caused by asphyxia.

I. Causes of asphyxia

The causes of asphyxia can be divided, from a morphologist's point of view, into three groups: cerebral, cardiac and pulmonary asphyxia.

1. *Cerebral asphyxia*.—Subdural hematoma above the tentorium may give rise to severe asphyxial symptoms. It is seldom lethal if diagnosed early and treated correctly. The most common complication is pneumonia. Subdural hematoma below the tentorium is rare and more difficult to diagnose. Leptomeningeal hemorrhages are probably not the cause of asphyxial symptoms. Intraventricular hematoma may be even lethal—it is usually found in premature infants only. Sometimes intraventricular bleedings are small and perhaps without clinical significance as a direct cause of asphyxia. Severe rupture of the tentorium with bleeding and symptoms of asphyxia is usually lethal.

Asphyxial symptoms of anencephalic monsters have been explained as caused by underdevelopment of their lungs. Some of these patients live

2-3 weeks without any asphyxial symptoms. Most congenital malformations of the central nervous system do not cause any asphyxial symptoms at all.

Some non-hemorrhagic changes in the brain tissue may cause asphyxial symptoms. Some newborn infants have severe symptoms pointing to the central nervous system without any morphological findings at autopsy. Hemorrhages and other changes in the medulla are rare.

2. *Cardiac asphyxia*.—The heart is a primary cause of asphyxia in cases of congenital malformation of the heart only. When this causes hypoxia of the brain, deficient pulmonary circulation, or mixing of venous and arterial blood, it is understandable that symptoms of asphyxia may develop. Myocarditis is rare in autopsy material of the newborn, but it can be the cause of asphyxia.

3. *Pulmonary asphyxia*.—Congenital atresias and stenoses of the respiratory organs are not often seen, but they may be the cause of severe asphyxia. A diaphragmatic hernia, although a rare malformation, is sometimes the cause of severe asphyxia from the first minutes of extrauterine life and should in these cases be diagnosed and treated early. Aspiration of amniotic fluid or mucus is one of the most common causes of asphyxia. The liquid part of amniotic fluid is rapidly adsorbed from the respiratory tract, but mucus and cells of amniotic fluid may block the airways and are therefore more dangerous. When precipitated protein is seen under the microscope in alveoli, it is not possible to say whether it is aspirated or edema fluid. This is one explanation of the differences of opinion over the value of pulmonary edema as a factor in respiratory difficulties of the newborn. Pulmonary hyaline membranes have been much discussed in recent years. They are most common in the first day and their incidence subsequently decreases, but they are seen in all age groups at autopsies. They have been found everywhere in the world at autopsies on the newborn when the lungs have been studied histologically. Many different theories exist about their genesis. For a pathologist and pediatrician it is difficult to believe that they could be without any clinical significance. It is possible to make a correct clinical diagnosis in most cases. These membranes are histologically different in different cases. It seems possible that the cause of membranes is also different. They may be caused by any factor damaging the pulmonary capillaries. In some cases they may be aspirated and in some cases brought there by the circulation. It is possible that local circulatory disturbances in the lungs may be a factor causing these membranes. They are seen at autopsies of full-term infants, too, and not only in babies of diabetic mothers, but in many different cases. In the writer's material the membranes were frequently seen together with pulmonary hemor-

rhages and pneumonias. This suggests that some factors in common may be involved in the genesis of these three conditions. Pneumonia is a fairly common finding at autopsies of the newborn. Congenital pneumonias are so rare that they are seldom the cause of asphyxia. Asphyxiated newborn infants easily develop pneumonia—as do all other newborn infants under bad conditions. The writer does not believe the old story that pneumonia would develop more easily in atelectatic than in air-containing lungs. This old theory has never been proved, neither has it any theoretical basis. Massive pulmonary hemorrhages were not a very common finding. Many of the babies had severe dyspnea before death. It is possible, but not proved, that massive pulmonary hemorrhage is due to the relative weakness of the left side of the heart of the newborn and to pulmonary congestion caused by heart failure.

II. Organ and tissue changes caused by asphyxia (or anoxia)

Opinions largely differ as to the changes caused by asphyxia in newborn infants. It is hardly possible to make a diagnosis of asphyxia on the basis of morphological findings alone. There are, however, several changes which may be consistent with anoxia. Combining these with the clinical history one may be able to make the diagnosis of asphyxia at autopsies on newborn infants. Congestion in different organs has been considered a sign of asphyxia. It is known that when a newborn or fetus is suffocated as a result of detachment of the placenta or placenta praevia, congestion and ecchymoses may occur in the organs of the thoracic cavity. When the infant or fetus dies as a result of a prolapse of the cord, these changes are not seen—and these babies, too, die in anoxia. Hence the diagnostic value of congestion is not very great in these cases. In German literature one can find as long ago as twenty years back experimental evidence that petechial hemorrhages do not show the cause of death and therefore are only of historical interest. Heavy aspiration of amniotic fluid is the best sign of fetal anoxia found at autopsy, but when it is lacking it does not exclude fetal anoxia.

It is reasonable to say that intraventricular cerebral hemorrhage is more likely to be caused by anoxia than by trauma—but one can ask whether this is enough to prove that it is really caused by anoxia. The same can be said about the leptomeningeal small hemorrhages often found at autopsies of newborn infants.

In the hearts of newborn infants, homogenization and even necroses of the walls of the coronary arteries are sometimes found. These changes may be related to anoxia. There seems to be some correlation between the clinical signs of asphyxia and the changes in the ECG. This question will

be discussed by Dr. LANDTMAN. Changes of myocardial damage have sometimes been observed by the writer; their diagnostic value, however, is not great.

The kidneys and the liver are organs which may be damaged by anoxia. Occasionally severe changes may be seen in the liver. There are some reports on degenerative changes in the right half of liver caused by anoxia. A fairly common finding at autopsies of newborn infants is fatty material in the cells of the collecting tubules of the kidneys. Simultaneously granular or hyaline casts may be found. The changes are mostly in the "lower nephron" but it is questionable whether these changes can really be called "lower nephron nephrosis". The diagnostic value and clinical importance of these changes is questionable.

Hemorrhages in the adrenals are at least partly vital, because one can also see old hemorrhages. The writer has seen a case in which a large adrenal hemorrhage gave symptoms of an abdominal tumour and was treated surgically with good results. Ulcerations in the gastro-intestinal organs may be related to anoxia. The most common is ulcerative esophagitis.

There are several other changes which indirectly may be related to anoxia. Much research is needed before the questions of the relationship between anoxia or asphyxia and changes in the organs of newborn infants are made clear. In this research pathologic anatomy will give its important contribution, when it is combined with clinical and laboratory studies.

Neonatal Asphyxia. Etiology and Pathogenesis

by WILHELM BLYSTAD, Norway

Etiologic and pathogenetic factors causing neonatal asphyxia can be comprised in four main groups: A, Malformations. B, Prematurity. C, Intra-uterine injuries. D, Extra-uterine injuries.

A. Malformations

Malformations of the brain, the heart, the respiratory tract, and the lungs can cause neonatal asphyxia. In these cases the problems will be of a mainly clinical, diagnostic and, occasionally, therapeutic nature.

B. Prematurity

The etiology and pathogenesis of respiratory disturbances in prematures still present many problems. The causes are often complex; different aspects of the prematurity may contribute to the development of the asphyxia.

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1. Immaturity of the respiratory center. The respiratory disturbances of the premature infant will frequently show characteristics indicating a failure of the respiratory regulation. Some authors have pointed out that this may be the result of immaturity of the respiratory center.

2. Incomplete development of the capillaries. This immaturity may be of a quantitative as well as qualitative nature.

Evidence of a reduced number of capillaries in the brain and in the lungs has been found, and it is supposed that a similar reduction may be present in the other tissues. A reduced number of capillaries in the tissues will interfere with the gaseous exchange between these and the blood. It is commonly assumed that there exists a hypoxia of the tissues; evidence of this is the high concentration of organic acids in blood and urine. In the lungs a lack of capillaries will be apt to cause a gradient of the oxygen tension from the alveolar air to the blood. It is further possible that the above-mentioned disturbances of the respiratory regulation are dependent on this tendency to hypoxia. From a general point of view; a tendency to Cheyne-Stokes' respiration will occur when the anoxia factor dominates the respiratory situation.

The fragility of the capillaries is increased in premature infants, and capillary microscopy has shown a different picture for prematures and for full term infants. Increased tendency to hemorrhage with intracranial and pulmonary bleedings can be pathogenetic factors causing respiratory disturbances.

3. Physical chemical factors. These are applicable to fullborn infants too, but will be more pronounced in prematures. A reduction of carbonic anhydrase in the blood and certain peculiarities of the dissociation curve of the oxyhemoglobin are concerned. These factors may contribute to the establishment of a hypoxia of the tissues.

4. Pulmonary hyaline membranes. In many cases of neonatal asphyxia the membrane formation seems to constitute an important link in the pathogenetic development. Etiology and pathogenesis are as yet obscure, but the relation to premature birth is clear.

5. Diminished or absent cough-and-swallow reflexes. A lack of these reflexes explains the greater risk of aspirating administered food or vomited gastric contents in premature infants.

C. Intra-uterine injuries

1. Intra-uterine asphyxia. Intra-uterine asphyxia may be the result of a number of different birth complications. This condition will cause injuries to the fetus, and thus bring about a persistence and further development

of the asphyctic state after birth. There may occur degenerative changes in the cells of the vital centres of the brain stem, causing a depression of these centres. The aspiration of amniotic fluid and its solid contents will further interfere with the inflation of the lungs. Asphyctic injuries of the capillaries will be apt to cause intracranial and pulmonary hemorrhage.

2. Toxic injuries. Anaesthetics and analgesics administered during the delivery will pass the placenta and affect the central nervous system of the fetus.

3. Intracranial hemorrhage following birth trauma. A hemorrhage will result in an increase of the intracranial pressure, and thus damage the above mentioned vital centres of the brain stem.

4. Infections. Pneumonic and septic conditions may arise from aspiration of infected amniotic fluid and from transplacental infection.

5. Lesion of *n. phrenicus* is a result of a complicated shoulder delivery.

D. Extra-uterine injuries

1. Injuries caused by resuscitation. These injuries used to be considerably more frequent than they are now. Of importance here would be injuries caused by vigorous manipulations, by mouth-to-mouth respiration, and by the use of resuscitators with over-pressure.

2. Aspiration may occur during feeding. Aspiration of vomited gastric contents would, however, be far more common.

3. Infections. In spite of modern precautions, extrauterine infections of the respiratory tract and of the lungs represent a significant factor for the establishment of asphyctic conditions in the neonatal period.

Asphyxia Neonatorum: Its Clinical Features and Treatment

by R. ZETTERSTRÖM, Sweden

Introduction

The symptoms observed in asphyctic newborn infants are due to a great extent to oxygen deficiency. It is more difficult to determine whether or not the often coincident increase in the carbon dioxide tension of the blood is also a contributory factor. In many cases of asphyxia of the newborn, severe hypoxia is already present at birth; the symptoms found post-natally are then only a result of the injury to the foetus *in utero*. Thus, extrauterine asphyxia is often a sequel of intrauterine asphyxia. It is known that various abnormalities and complications during pregnancy and labour

may be the essential cause. It has also been fully established —particularly by the comprehensive investigations of SMITH—that various types of anaesthesia not only depress the respiration of the newborn infant, but that some degree of intrauterine hypoxia may also arise. It has been shown by BARCROFT that intrauterine hypoxia, leading to death of the foetus, occurs in experimentally induced post-maturity in animals. The cause appears to be a degeneration of the placenta. The existence of similar conditions in man has recently been demonstrated by WALKER & TURNBULL. They found that the oxygen saturation of the cord blood fell extremely rapidly after term. After four weeks' post-maturity, it had fallen to the same low level as that in manifest eclampsia. The coincident increase in the oxygen capacity indicates that the decrease is not an acute phenomenon, but that it is of such long duration that polycythaemia has had time to develop. There are many indications that the tendency to attacks of asphyxia, which is present in some babies of diabetic mothers, is to be ascribed to intrauterine hypoxia. In this condition, the clinical features exhibit great similarities to those in haemolytic disease of the newborn, in which intrauterine anaemic anoxia usually occurs.

Premature infants and those delivered by caesarean section may, immediately after birth, exhibit symptoms resembling those found in babies who have suffered from intrauterine hypoxia. But, the infants in the former category have, at the actual moment of birth, the same oxygen saturation as full-term normal babies born in the natural way. Thus, in many of these cases, the asphyxia is purely post-natal. In premature infants, the deficient maturity must play a considerable role in their tendency to asphyxia. In infants delivered by caesarean section, it is improbable that the anaesthesia is the only contributing factor; there must also be some other cause.

Clinical Features

General features.—The symptoms found in asphyxia neonatorum are due to the hypoxia. Owing to the poor oxygenation of the central nervous system, a cerebral respiratory insufficiency develops. The tissue anoxia in the myocardium leads to circulatory insufficiency. These two factors cause changes in the respiratory tract and in the lungs, which aggravate the respiratory embarrassment. Unless the asphyxia can be arrested, the condition deteriorates successively and death takes place. The combination of respiratory and circulatory insufficiency rapidly leads to severe tissue damage. The blood flow in various organs decreases, at the same time that the oxygen saturation of the blood flowing through the tissues becomes increasingly lower. Both anoxic anoxia and stagnant anoxia develop.

Signs of circulatory insufficiency.—In the milder cases, cyanosis is the only symptom of hypoxia. If hypoxia increases, circulatory insufficiency appears. The electrocardiographic changes which are found in asphyxia neonatorum, and which have been studied by ÅKERRÉN, indicate the presence of severe myocardial damage. There is also an abnormal increase in the heart volume. Under normal conditions, the average decrease in the heart volume during the first two days of extrauterine life amounts to about 25 per cent. In asphyxia neonatorum, this decrease fails to take place as long as the symptoms of asphyxia persist. As soon as the asphyxia subsides, however, a very rapid reduction in the heart volume also occurs in these infants. With the appearance of severe circulatory insufficiency, the arterial blood pressure falls considerably, whereas the venous pressure rises. These manifestations are most conspicuous in the presence of pallid asphyxia.

The blood flow through the kidneys is decreased, owing to the circulatory insufficiency. Oliguria and extrarenal azotaemia appear. Moreover, the tissue anoxia presumably also causes direct damage to the renal parenchyma, and the condition denoted by JONSSON as "lower nephron nephrosis in asphyxia neonatorum" develops.

Inhibition of the activity of the central nervous system.—The paralysis and possible damage to the central nervous system are the most serious features as far as the future course is concerned. The hypoxia and circulatory insufficiency lead to decreased metabolism in the central nervous system. The ability to react to the responses which elicit the respiratory movements is impaired or arrested. The central regulation is further depressed by the fact that the tissue anoxia more or less directly leads to a tendency to oedema, as well as to the occurrence of petechial haemorrhages. This tendency is particularly marked in premature infants and in babies born to diabetic mothers, but may also occur under other conditions. In the presence of oedema, the symptoms are fairly similar to those in intracranial haemorrhage. The infants behave in the same way. The rise in pressure causes increased tension in the fontanelles. The protein content of the cerebrospinal fluid is usually increased. There is often a relative increase in the bilirubin content of the C.S.F., a symptom which seems to indicate damage to the blood-brain barrier. Naturally, it is extremely difficult in many cases to determine whether or not brain damage is the primary cause of the asphytic condition.

Changes in the respiratory tract and lungs.—In every case of asphyxia neonatorum, pathological changes are present in the lungs and air passages. During foetal life, the air passages are filled with amniotic fluid. If anoxia develops during labour, this fluid seems to be drawn deeper into the lungs through aspiration, instead of being resorbed and disappearing.

Resorption is impaired, on the grounds of the circulatory insufficiency. There is also evidence to show that the asphyctic condition causes an abnormal increase in the secretion of mucus, a complication which must contribute still further to impairing function of the lungs. It seems to be established that it is not only aspiration, but exudation as well, which causes the appearance of so-called hyaline membranes, which constitute the most serious respiratory tract complication during the neonatal period. Hyaline membranes are particularly apt to appear in premature infants, in babies born to diabetic mothers and in those delivered by caesarean section. In other words, they develop in children in whom there is either a tendency to oedema, or in whom it may be assumed that resorption of the fluid which fills the air passages has not started at birth.

Metabolic disturbances.—The generalized tissue anoxia results in acidosis. This must also be due to a great extent to the carbon dioxide retention which is a result of the impaired gas exchange in the lungs. It is not invariably associated with a decrease in the alkali reserve, and its degree can be evaluated only after determination of the pH of the blood. There is no decrease in fixed base.

Diagnosis and Complications

In asphyxia neonatorum, the symptoms are due essentially to the respiratory distress, to the circulatory insufficiency and to the cerebral involvement. In some cases the respiratory tract symptoms predominate, and in others the cerebral symptoms. The difference is probably to be ascribed to the conditions under which the asphytic condition has developed, to the degree of hypoxia and to the degree of maturity of the infant.

Difficulties are encountered in distinguishing between this condition and brain damage. Presumably, intracranial haemorrhages can also occur as a result of asphyxia. When signs of circulatory failure predominate, it may often be hard to distinguish the primary asphytic condition from a primary circulatory insufficiency on a cardiac basis (e.g. paroxysmal tachycardia). Another fact which makes the differential diagnosis more difficult is that a murmur is frequently heard in the presence of anoxia. A continuous murmur, which can often be recorded, seems to be dependent on the fact that functional closure of the ductus arteriosus does not take place when there is severe hypoxia. The murmur disappears after the administration of oxygen. Obstructions or malformations of the respiratory tract and lungs may present great clinical similarity to primary asphyxia neonatorum. If a thorough examination is made, it is usually possible to diagnose such conditions as choanal atresia, the syndrome of cleft-palate and microgenia, a

laryngeal obstruction or atresia of the oesophagus. Radiological examination of the respiratory tract and thorax seems, however, to be the most certain means of diagnosing the presence of anomalies of this nature. Consequently, a radiological examination should be made routinely in every questionable case of asphyxia neonatorum.

Atelectasis of varying degree is a constant finding in asphyxia neonatorum. The extent is best determined by means of radiological examination. Atelectasis may be primary, i.e., the lung parenchyma has never been aerated, or it may be secondary, i.e., resorption atelectasis. The latter type develops as a result of bronchial occlusion caused by, for example, the aspiration of plugs of mucus, or exudation into the finer branches of the bronchi. Atelectasis is most extensive after the formation of hyaline membranes. Bronchostenoses may act as valves and cause distal rises in pressure, with resulting interstitial or subpleural emphysema. This, in turn, may lead to spontaneous pneumothorax and mediastinal emphysema, which are not infrequent complications. They have been observed both as a result of more localized bronchostenosis, and as a complication of hyaline membranes. The onset of these complications is sudden. There is an acute systemic effect; the infants show signs of extreme air hunger, and the symptoms of circulatory insufficiency are conspicuous. Convulsions are often seen. Bronchopneumonia also seems to be a common accompaniment of an asphyctic condition, and the tendency to this complication must be particularly great when the amniotic fluid has been infected. It is also probable that pulmonary and adrenal haemorrhages may occur as a sequel of asphyxia neonatorum.

Treatment

The primary aim must be to arrest the hypoxia. In order to make maximum use of the irregular respirations and the still functioning lung parenchyma, oxygen is given in as high a concentration as possible. It may also be possible to increase the oxygenation of the blood by means of gastrointestinal oxygen insufflation or the injection of oxygenated blood. During the apnoeic periods, the administration of oxygen to which 5 per cent carbon dioxide has been added must be regarded as contraindicated. The carbon dioxide tension of the blood is so high initially, that this mixture is more apt to depress the respiration than to stimulate it. In hyperventilation, on the contrary, oxygen with 5 per cent carbon dioxide may be indicated in order to counteract the alkalosis.

Everything should be done to ensure a free airway. Owing to the asphyxia, the production of mucus is greater than in normal newborns. Energetic procedures such as the introduction of a bronchoscope should, how-

ever, be avoided, since the subsequent swelling of the mucosa may aggravate the condition still further. It seems possible to prevent exudation into the air passages to a certain extent by allowing the infant to inhale a gas mixture with a high degree of moisture. Good results have been reported with the use of mist.

Many experiments have been made to determine the position which is most suitable for facilitating the respiratory movements. In some cases, the position most favourable to the respiratory movements has nevertheless had the drawback of hampering the circulation in the central nervous system. Various types of slings and respirators have been constructed. According to recent experiences, the insufflation of oxygen under positive pressure may be of value, provided that the procedure is carried out by trained staff. If, on the contrary, this method is used without adequate control of the pressure applied, and without careful, individual consideration of every case, complications are likely to ensue.

The infant should be undisturbed to the greatest possible extent. No food should be given by mouth. This is in order to decrease the tendency to vomiting and the risk of aspiration. Moreover, the respiration is not impeded by distension of the stomach. Continuous drip infusion into the stomach has been tried with good results in premature babies. In many cases, it may also be suitable to empty the stomach as soon as possible.

It is unquestionable that various types of skin stimulation are of great importance in promoting respiration. On the other hand, it is highly doubtful whether such violent methods as contrast baths have any justification. The measures that are justified are those which, without injuring the infant, help to arrest the circulatory insufficiency and to increase the gas exchange in the lungs. In the light of recent experience, it seems that good results may be obtained by means of a moderate reduction in the body temperature. By this means, the oxygen consumption is decreased, and this is presumably of particularly great value in severely dyspnoeic infants.

Since pneumonia easily develops in the atelectatic lungs, anti-infective therapy seems to be indicated. Obviously, it is then necessary to take into consideration the pathogenic organisms which are likely to cause infectious complications.

It is not yet altogether certain whether the central regulation of respiration can be stimulated by drugs in an asphyctic condition. A subcutaneous injection given to a baby with marked circulatory insufficiency can scarcely have any immediate beneficial effect. This is because resorption is greatly retarded. Consequently, if any effect is to be obtained, intravenous injection is indicated. There is, however, a considerable risk of intoxication.

Our knowledge of many aspects of asphyxia neonatorum is still far from

complete. It is therefore impossible at present to draw up any hard and fast principles of treatment. I nevertheless hope that we shall be able, in the course of the subsequent discussion, to arrive at a more uniform scheme of treatment in this condition.

On the Combined Effect of Circulation and Respiratory Movement During Lung Expansion in a Newborn Infant

by S. JÄYKKÄ, Finland

Physiological experiments with the lungs of stillborn infants in a specially constructed apparatus. The experiments seem to indicate that in the mechanism of lung expansion the changing of the prenatal circulation into postnatal plays a decisive role. To be published later in *Acta Paediatrica*.

Some Facts Concerning the Pathogenesis of Hyaline Lung Membranes

by R. BERFENSTAM, Sweden

We know that hyaline lung membranes can be provoked in animals in various ways, amongst others with the aid of highly concentrated oxygen. Experiments on adult rabbits kept for 4–5 days in 70–80 per cent oxygen show membranes in about 80 per cent of the exposed animals. Histologically these membranes show a picture that well agrees with that found in newborn infants.

An attempt to explain the origin of these experimentally produced membranes gave rise to the idea of investigating the ciliary transport function in the upper air-passages of animals exposed to oxygen. In the course of this investigation the speed of transport of siliconized carbon particles on the tracheal membrane was measured. A comparison with normal material showed that the ciliary transport after oxygen treatment had ceased completely in more than half the cases, while transport was patchy and irregular in the remainder.

What significance the stagnation of secretion may have for the origin of membrane growth cannot be judged with any certainty. If these experiments have their counterpart in natural conditions, however, it is plain that a lengthy and fairly intense oxygen treatment of newborn infants may for this as well as other reasons have harmful consequences.

Electrocardiographic Studies of Asphyxia Neonatorum

by B. LANDTMAN and E. K. AHVENAINEN, Finland

Electrocardiograms were taken of 122 asphyxiated newborn infants. Fifty-nine infants who did not show clinical signs of asphyxia were used as controls.

The electrocardiograms were considered normal in 51 cases in the control group. Iso-electric or flat T waves were recorded in 4 instances.

Seventy-nine of the asphyxiated infants showed abnormal electrocardiograms. Flat, inverted or diphasic T waves were the most common abnormality.

Twenty-eight of the asphyxiated infants who showed pathological T waves were followed up by series of electrocardiograms. In all but one of these cases the electrocardiogram became normal. There was a positive correlation between the changes of the T waves to normal and the clinical recovery of the patients from the asphyxia. The serum potassium level, determined in a few instances, was normal.

It is suggested that the T wave changes in the electrocardiogram were a direct or indirect anoxic effect. Evidence is presented that these changes may serve as an aid in the diagnosis of neonatal asphyxia and in prescribing adequate treatment.

An Experimental Study of the Human Fetus with Special Reference to Asphyxia Neonatorum

by BJÖRN WESTIN and GÖRAN ENHÖRNING, Sweden

The outcome of asphyxia neonatorum is often indeterminable and unexpected. Hence, very long apneic periods can be followed by spontaneous breathing without any therapeutic measures. On the other hand, asphyxia can suddenly lead to post-natal death without the infant showing signs of any other disease. In view of these facts it seems to be difficult to draw any definite clinical conclusions in treating asphyxia neonatorum without objective methods of registration. As circulation may be deeply impaired, there is reason to assume that the *transport* of oxygen by the conventional methods, i.e. from the skin, the airways or the gastro-intestinal canal to vital centres, is considerably slower in deep asphyxia than in the healthy newborn. Even if the tolerance for anoxia in the newborn is high,

the insurance of an adequate supply of oxygen to the respiratory centre is considered to be the most important step in the treatment of asphyxia neonatorum. To achieve this, heart activity must quickly be improved and circulatory insufficiency eliminated.

The observations we have recorded below are intended primarily to show more closely the effect of oxygenated blood on heart activity, blood pressure and respiratory movements in preivable human fetuses. The tests were performed on fetuses ranging in length from 12–34 cm and obtained from 14 legally induced and 23 spontaneous abortions. Blood pressure registered in one of the umbilical arteries and the ECG were studied continuously until signs of heart activity ceased.

Briefly, the following results were obtained:

1. In seven *untreated* fetuses a rapid decline in heart rate and blood pressure was noted. Simultaneously, a lengthening of conduction time and S-T interval were recorded. The height of the T-waves rapidly declined and turned negative within an hour. By means of a catheter introduced into the ductus vein. Arantii it could be shown that primitive respiratory movements improved circulation by accelerating the venous return to the heart. At the same time a temporary decline in arterial blood pressure was noted. Recorded at an air temperature of 25° C, cessation of heart activity occurred between the third and fourth hour after delivery. At an air temperature of 25° C, the rectal temperature of the fetuses fell to 30° C within 10–15 minutes. At an air temperature of 37° C, the fetuses survived only between 1–1 1/2 hours indicating that in human fetuses survival time is lengthened when temperature is lowered.

Oxygen and carbon dioxide tension in the umbilical vessels has been determined according to SCHOLANDER-RILEY. Oxygen tension in the umbilical vein rapidly declined and carbon dioxide tension in the umbilical arteries soon reached extremely high values. For example, ten minutes after birth, in legally induced abortions, the oxygen tension in the umbilical vein was about 20 mm Hg and the carbon dioxide tension in the umbilical vein was about 50 mm Hg. In the umbilical arteries the corresponding values were from 0–3 mm and about 90 mm Hg, respectively.

2. In asphyxiated *treated* fetuses the following results were obtained. Five per cent glucose or physiol. sodium chloride solution, injected into the umbilical vein, had hardly any effect on heart rate or blood pressure. This was also true of venous citrate blood. Moreover, a permanent lengthening of conduction time was recorded. On the other hand, 2–3 cc of oxygenated citrate blood improved circulation within a few moments, although heart rate and blood pressure could not be completely normalized. Moreover, the S-T intervals were lengthened and the T-waves abnormally high. This

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effect on the ECG is probably mainly due to hypocalcemia. Hence, large doses of citrate solution or oxygenated citrate blood considerably shortened survival time. The intravenous injection of equal amounts of oxygenated heparin blood, however, normalized ECG, heart rate and blood pressure as late as 1 1/2 hours after birth. Oxygenated citrate and heparin blood, in doses of 2-4 cc, produced "gasps" as late as 45 minutes after birth, when injected in the umbilical vein.

Single injections of 0.05 mg noradrenaline in the asphyxiated fetus, immediately brought about pathological changes in the ECG similar to those found in adults in coronary thrombosis.

In agonal states of the fetuses, oxygenated heparin blood injected into the umbilical vein failed to restore heart activity and blood pressure. By injecting 5-10 cc oxygenated heparin blood into one of the umbilical arteries a rapid increase in heart rate and blood pressure was recorded and the pronounced pathological changes in the ECG were considerably improved. In a few cases, gasps were produced in connection with the injection.

3. The effect of oxygenated heparin blood on heart rate, blood pressure and primitive respiration in the asphyxiated human fetus would seem to indicate its value in reviving newborn infants. Clinical tests proved that viable deeply asphyxiated newborn infants could be revived by the transfusion of oxygenated blood where the conventional treatment produced no effect.

In agonal states of the newborn the intraarterial transfusion would seem to be indicated, although clinical experience is still lacking.

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Which Method Should Be Chosen for the Treatment of Asphyxia?

by YNGVE ÅKERRÉN, Sweden

Anoxia and respiratory insufficiency are of dominating pathogenetic importance with asphyxia in the newborn infant. Close interaction exists between these factors in the form of circulus vitiosus mechanisms. In

active therapy, a supply of oxygen is the most important factor. The method chosen should be simple, effective, and rapid. The gastro-intestinal technique elaborated in Gothenburg reasonably covers these demands in cases of severe or moderate asphyxia. The treatment can be given even without the presence of a physician.

In cases of slight asphyxia or when a severe case is improving, the supply of oxygen is given through a tube enclosed in a funnel-formed mask. An increase in the amount of oxygen in the inspiration-air, and stimulation of the skin and the mucous membrane in the trigeminal region, are thus acquired. The technique is based on theoretical and practical investigations by BARCROFT. It is also suitable for immature infants with attacks of apnoea.

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The Practical Organization for the Care of Asphyxiated Infants in the Maternity Clinics in Gothenburg, Sweden

by K. HOLMDAHL, Sweden

Combating asphyxia in newborn infants is not only a scientific problem but also one of organization. Effective and rapidly functioning co-operation between two different specialities, which frequently work in different hospital departments, is needed.

Particularly during recent years, we have attempted to improve this organization in the maternity departments in Gothenburg and, simultaneously, we have observed a diminished mortality among newborn infants. Although, naturally, it is impossible to determine to what extent the measures mentioned have played a part, the result is, however, encouraging and the organization has functioned satisfactorily. As the maternity department is, in addition, relatively large with approximately 4,000 deliveries per annum, we consider an account to be of general interest.

Among 3,262 full-time newborn infants in 1953, 110 (3.4 %) suffered from extra-uterine asphyxia and among 153 premature infants, 38 (24.8 %) suffered from extra-uterine asphyxia. In addition to this higher incidence of asphyxia, it is noticeable that in premature infants the risk of the so-called late asphyxia is greater. Three categories among the full-time infants may, in respect of the risk of asphyxia, be considered comparable

Table 1
Care of the asphyxiated premature infant

	Prior to delivery	During delivery	After delivery	During neo-natal period
Prophylaxis	Good prophylactic maternal care, particularly prophylaxis of anaemia.	1. Analgetics and sedatives administered with restraint. 2. No anaesthetic in any form. 3. No oxytocic drugs. 4. Oxygen to mother. 5. Prophylactic episiotomy. 6. Antibiotics etc. to mother.	Special care immediately after delivery: 1. Aspiration and emptying of stomach. 2. Oxygen via funnel. 3. Control of temperature and institution of hibernation. 4. Transfer to special department.	Special 24-hour care: 1. Strict observation. 2. Hibernation. 3. Special attention paid to nutrition. 4. Routine antibiotic therapy.
Treatment	Slight asphyxia	—	Oxygen to mother	Special care immediately after delivery: 1. Aspiration, emptying of stomach. 2. Skin stimulating measures. 3. Oxygen via funnel or in incubator (with care).
	Severe asphyxia	—	Termination of delivery as rapidly as possible.	Special care immediately after delivery: 1. Aspiration, emptying of stomach. 2. Gastro-intestinal oxygen. 3. Endotracheal insufflation.

with premature infants: postmature infants, infants of diabetic mothers, and infants whose delivery was complicated in some respect (Caesarean section, infants who showed signs of intra-uterine asphyxia, infants born after complicated breech delivery, forceps etc.).

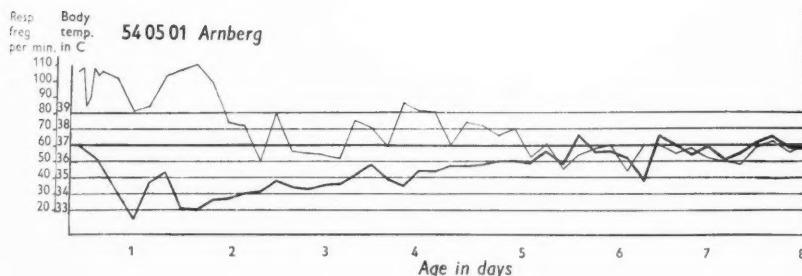
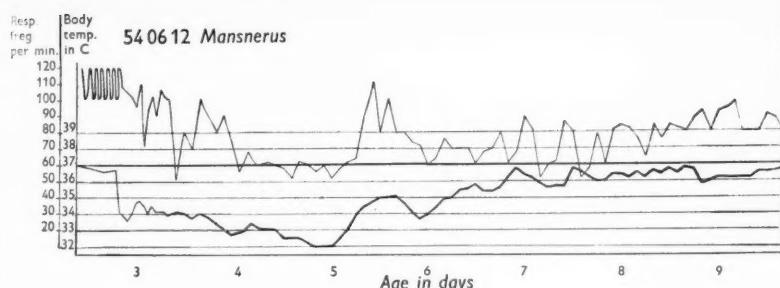
Table 1 shows the prophylaxis of asphyxia and the treatment of premature infants. These principles are also suitable, when feasible, in the care of the categories of full-time infants mentioned above. The following viewpoints are considered to be of special significance in the prevention and treatment of asphyxia in newborn infants:

1. Intimate co-operation between obstetricians and paediatricians so that the infant is considered already during the delivery, in particular, premature infants and those full-time infants whom experience has shown to be most threatened by asphyxia.
2. Paediatricians take over the responsibility for the care of newborn infants immediately after delivery. Special attention is thereby paid to the categories mentioned.
3. Special departments should be available, in any case in the larger maternity departments, where infants threatened by asphyxia and asphyxiated infants may be admitted for special observation and care.
4. Well-trained nurses undertake the immediate responsibility for the care of the asphyxiated infants.

Discussion

P. Karlberg, Sweden.—Studies of the respiration in early infancy, partly on normal infants, partly on infants threatened by respiratory insufficiency have been undertaken. These investigations are presented to the Congress in the form of a scientific exhibition and will be published in *Acta Paediatrica*. All the pathological cases presented the following clinical picture: During the first day of life there was progressive and severe dyspnoea with a high respiration rate and cyanosis in any case in atmospheric air. The respiration sounds were laboured, and there were many and scattered adventitious sounds. X-ray examination of the lungs showed numerous scattered opacities. In brief, the signs of an increasing lung insufficiency were present—a symptom complex constituting a well-defined group included in the general term asphyxia neonatorum. We call it “respiratory distress”. In the acute stage our investigations showed an increased ventilation (min. volume) mainly caused by increased respiration rate. Tidal volume practically normal. CO₂ being within normal limits, the cause of the increased ventilation must be sought in an abnormal gas exchange. The alveolar ventilation (i.e. the total ventilation of those parts of the lungs where the gas exchange takes place) within normal limits or possibly somewhat low. The functional dead space increased, which may be a sign of changed anatomical conditions, changed ventilation conditions or a change in the conditions of the circulation in the alveoli—or, most likely, a combination of these factors.

The intra-pleural difference in pressure between inspiration and expiration (determined by the intra-oesophageal pressure differences) showed values 2 to 5 times increased. This indicates a diminution of the elasticity of the lung tissues. The total ventilation being also increased, the work of



respiration for these "respiratory distress" infants becomes 4 to 10 times greater than normal. Much research work is still needed before we can fully understand the patho-physiology of these "respiratory distress" infants.

It is, however, obvious that this greatly increased work imposed on the respiratory system is of great clinical importance. Clinicians have long realized that the clinical picture presented by infants who die of "respiratory distress" reflects a general physical exhaustion contributing greatly to the fatal issue. They cannot manage to keep respiration going in combination with an ever-increasing respiratory insufficiency.

With these considerations in mind, we have begun at Karolinska sjukhuset in Stockholm to try to help "respiratory distress" infants in the severe and acute stage of the disease by reducing the claims made on respiration. This is done by reducing the body temperature and thereby the metabolism of the tissues. These cases have had progressive respiratory difficulties, where the physical claim made on the infant to maintain a somewhat sufficient respiration, in its widest connotation, has approached

the child's limit of endurance, not only judged by the general clinical status, but primarily by the respiration frequency. Our above-mentioned observations seem to show that a respiration rate of 100–120 per minute represents the maximum capacity.

The infants have been kept in an incubator, and their body temperature has been lowered by reducing the supply of heat to the incubator. With the lowered body temperature there has been a general improvement and a fall of the respiration rate was obtained (see figure). This fall of the body temperature has been graduated so that the respiration rate was kept at a level between the maximum and the normal in order to retain a certain extra forcing of the air expansion of the lungs, thus promoting the return of their functions to the normal. This means that, as the infant begins to recover, the body temperature can gradually be raised towards the normal level (see figure). We have had the definite impression that severe cases of "respiratory distress" have benefited from this hypothermic treatment. The investigations of this method are being continued.

C. E. Räihä, Finland.—The CO₂ retention in the blood of the newborn would seem to be connected with the volume of the haemoglobin-bound CO₂. The CO₂ content of the umbilical vein is about 41 vol. %. According to ÖSTERLUND, the CO₂-content of the corresponding plasma is about 22 vol. %, or half that of the CO₂ content of the blood. As the water content of blood corpuscles is lower than in plasma, some CO₂ must be haemoglobin-bound, and an increased oxygen content of the blood should decrease this fraction.

K. H. Torp, Norway.—The prophylaxis is of importance in the problem of asphyxia neonatorum, and specially the prevention of lung infection as cause of the asphyxia.

To throw light on this matter, reference was made to 60 cases of pneumonia in newborn infants examined post mortem at the Rikshospital in Oslo. They consisted of 16 cases of still-birth associated with pneumonia (Group A), and 44 cases of pneumonia terminating fatally during the first 3 days of life.

The 16 still-born infants suffering from pneumonia were *exceptionally large infants*, the mean weight at birth being 3.9 kg as compared with 3 kg for 153 still-born infants without demonstrable pneumonia. The mean weight at birth of the 44 infants in Group B was 3.15 kg as compared with 2.9 kg for the 110 infants who died during the same interval without demonstrable pneumonia.

Among the 16 mothers in Group A there were 12 elderly primiparae (more than 28 years of age).

Among the 44 mothers in Group B there were 24 more than 28 years old, and in 16 of these cases the course of the confinement, or the early clinical picture of disease presented by the infant, or the massive changes in the lungs found at the post-mortem examination gave grounds for assuming the existence of pneumonia acquired during intra-uterine life. Among these 16 infants whose pneumonia was probably of intra-uterine origin, there were 9 whose weight at birth was over 3.9 kg.

Conclusion.—Pneumonia acquired during intra-uterine life is a birth-complication which seems to be specially common when elderly mothers—often elderly primiparae—give birth to an exceptionally large infant.

It is particularly to this definite category of mothers that it seems we must apply prophylactic measures (obstetrical, antibiotic). Further, particularly large infants suffering from asphyxia should in principle receive prophylactic antibiotic treatment, which seems to be quite specially indicated when the mother is an elderly primipara, independent of the available information regarding the course of her confinement.

We cannot rely on such information as "a normal confinement" when we are confronted by this combination of an elderly mother and a large or post-mature infant, and we cannot very often expect to find a clinical examination, a blood report or a radiological finding giving decisive information as to the presence of pneumonia in a newborn infant.

V. Rantasalo, Finland.—If we increase the intra-peritoneal pressure by oxygen insufflation to the intestines, the work of the diaphragm will be embarrassed, and it will not be easy to set normal expiration in motion. When physiological respiration does not function in a satisfactory way, the discharge of CO₂ from the blood becomes inadequate, with the result that the blood's CO₂ rises. The physiological stimulation of the respiratory centre is changed and does not act as in normal conditions.

P. W. Braestrup, Denmark.—Six cases have been observed of drug poisoning of newborn infants given nicetamid (coramin) or cardiazol to stimulate respiration. The doses, readjusted to correspond to a body-weight of 75 kg, were about 20–45 ml, corresponding to up to 3.5 convulsion doses.

The use of drugs belonging to this group is to be avoided as the indications for them are not clear, and the pamphlets and instructions for their use give doses which are dangerous for neonatal asphyxia treatment.

Y. Åkerrén, Sweden.—With reference to Professor Rantasalo's remarks, I would like to raise two points: (1) The double catheter, with its afferent tube which serves as a safety-valve, should be an effective prevention of

a too great rise of intra-abdominal pressure. The anus also serves as a safety-valve. Further, interruption of the supply of oxygen may be indicated when considerable abdominal distension is observed on inspection. (2) The direction of the exchange of gas between the contents of the intestines and the blood is determined partly by the gradient, partly by the rate of diffusion of the respective gases. Animal experiments have shown that when pure O₂ is injected into an isolated coil of intestine, with circulation retained, CO₂ diffuses over from the blood to the contents of the intestine. We should note that if the treatment of asphyxia is really effective, the response is prompt, with the result that respiratory movements are started, and the surplus of CO₂ can be rapidly eliminated through the lungs. In asphyxia neonatorum we are dealing with an acute anoxia situation, and it is therefore not analogous to the situation arising on artificial respiration undertaken for anoxia in poliomyelitis.

A. Sundal, Norway.—As already pointed out, pathological changes exist in the respiratory passages in every case of asphyxia neonatorum. The respiratory passages contain fluid at birth, and in cases of asphyxia this fluid is drawn during delivery further down the pulmonary tract. The secretion of mucus increases in the respiratory tract and there is also probably some exudation. The hyaline membranes which play such important a part for premature infants probably depend on several of these factors. Whatever the causes, it is important to see that, if possible, the fluid in the respiratory passages does not become less liquid. Our object is in this way to prevent the formation of these membranes. The enzymes in Varidase are capable of acting on fibrin, fibrinogen and nucleo-proteins, and it would seem to be rational to apply a varidase spray to newborn infants who are markedly premature and who are very predisposed to hyaline membranes. At The Children's Hospital in Bergen we have applied a Varidase spray during the last half year to all the premature infants with a weight at birth under 1,500 g, and to newborn infants with signs of asphyxia. Quite empirically we have given a spray for 2 minutes every half hour—an ampoule containing 25,000 units dissolved in 10 ml sterile water, so that about 1,000 units (about 0.5 ml) are given every half hour. While the infant is being sprayed, the nurse tries to assure the best possible respiratory movements for the infant, the spray being held close to the nose and mouth. The premature infant is at the same time treated in an incubator with oxygen and a relative humidity of approximately 100 per cent in the incubator.

Our experience is too small to warrant the presentation of results. We have neither hitherto found a method to show whether the Varidas-

treated infants who subsequently die have got Varidase introduced far enough down into the lungs so that it comes into contact with the material which changes to membranes later on. We have, however, the impression that this spraying has had a favourable effect, easing respiration and diminishing asphyxia. We have not seen any side effects.

P. Karlberg, Sweden.—In his account of the organization for dealing with asphytic infants in the maternity hospitals in Gothenburg, Dr. Holmdahl classifies cases of asphyxia according to the different degrees of severity, and he recommends suitable methods of treatment for the different groups. In the most severe cases the treatment consists of intubation of the trachea. In well-trained, careful hands this seems to be radically effective.

At the Karolinska sjukhuset in Stockholm we have with newborn infants suffering from pulmonary atelectasis and respiratory insufficiency begun to try a careful insufflation under positive pressure through a face mask or tube in the pharynx, with mouth and nose temporarily closed. From many quarters warnings have been given with regard to this method, primarily because of the risk of lung parenchyma damage with a pneumothorax among other things as the result.

The reason why we have adopted this method is to be found in RICHARD DAY's investigations in New York. He has shown by experiments on atelectatic lungs of the newborn that by giving positive pressure treatment in the form of repeated, very brief (0.20–0.10 seconds' duration) pressure impulses (automatically controlled with regard to both pressure and time, but manually started on each occasion) a good effect has been obtained, but at the same time with a much reduced risk of parenchyma damage. With this method he was able to employ as high a pressure as 40–50 cm of water. The commercially available apparatuses employ a pressure only of about 20 cm of water—a pressure which his experiments showed was usually ineffective on the atelectases.

In some cases of severe and extensive pulmonary atelectases we have tried insufflation at repeated and very short intervals. Radiological examinations immediately before and after this treatment have shown a certain clarification of the opacities without any apparent damage to the lung parenchyma. We are now engaged on the construction of an apparatus where the pressure and the interval of time for these pressure impulses can be easily controlled. We shall continue to test the usefulness of this method in those cases of severe and extensive pulmonary atelectases in which other methods have not yielded satisfactory results.

K. Holmdahl, Sweden.—Endotracheal insufflation appears to be a valuable procedure in the treatment of severe asphyxia. Correctly employed, the method is practically without risk. For some time prophylactic tracheotomy was employed as a routine measure in the Children's Hospital in Gothenburg in co-operation with our anaesthetist Dr. G. Haglund. Despite prolonged positive pressure respiration with pressure control, in some cases for a couple of months, no traumatic pulmonary complications were encountered.

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General Meeting of the Northern Pediatric Association on July 1st, 1954

An account of the financial status of the association was given by the former Secretary General, Dr. JUSTUS STRÖM, Sweden.

After the retirement of Professor WALLGREN, Sweden, the following new board were elected:

Denmark

Professor P. PLUM
Professor OLUF ANDERSEN
Dr. A. ROTHE-MEYER
Dr. E. W. FLENSBORG, substitute.

Finland

Professor C. E. RÄIHÄ
Professor T. SALMI
Docent P. HEINIÖ
Docent N. HALLMAN, substitute

Norway

Professor L. SALOMONSEN
Dr. A. NJÅ
Professor A. SUNDAL
Dr. R. RINVIK, substitute

Sweden

Professor S. SIWE
Docent J. STRÖM
Professor B. VAHLQUIST
Professor Y. ÅKERRÉN, substitute.

Auditors: Dr. HANNA BERGHOFF, Norway and Dr. S. LAHDENSUU, Finland. *Substitutes:* Dr. E. GJÖRUP, Denmark, and Docent B. BROMAN, Sweden.

At the motion made by the Board, the general meeting decided that the next congress be held in Helsinki in 1958. Professor C. E. RÄIHÄ was elected president of the next congress.

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Scientific Exhibition

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Endocrinology

The Problem of Child Diabetes in Finland

by OLLI SOMERSALO

The Central Hospital in Joensuu, Finland

Chromatographic Studies of the Excretion of Ketosteroids in Children with the Adrogenital Syndrome

by C. G. BERGSTRAND, G. BIRKE and L. O. PLANTIN

Kronprinsessan Lovisa's Children's Hospital, Stockholm, Sweden

Method.—(1) Preliminary fractionation of the urinary ketosteroids according to ZYGMUNTOWICZ *et al.* (1951); (2) Further separation of the steroids by a system of columns with magnesium silicate and aluminium oxide (PLANTIN and BIRKE, 1954); (3) Identification of the different ketosteroids by infra-red spectrography.

Results.—Six patients with the adrenogenital syndrome were examined. The chromatographic patterns of urinary ketosteroids were compared with those obtained in normal adult men, in normal children of the same age and in a patient with sexual precocity caused by a cerebral tumor. The chromatographic patterns of five of the patients (4 boys with macrogenitosomia praecox and 1 girl with pseudohermaphroditism) were almost identical and very much like those seen in normal men. By infra-red spectrography it was shown that in the cases of adrenogenital syndrome, ketosteroids were excreted which normally are not found in the urine. One boy had adrenal insufficiency but no difference in the chromatographic pattern was found when this patient was compared with the other cases of adrenogenital syndrome. A newborn girl with pseudohermaphroditism had a different type of chromatographic pattern and no ketosteroids could be identified in her urine. The reason for this is unknown. In the patients who received cortisone the chromatographic patterns were "normalized" during treatment. The chromatographic pattern from the boy with sexual precocity caused by an intracranial tumor was different from those obtained in the patients with adrenogenital syndrome.

Skin Biopsy and Thyrotropin Assay in Children with Endocrine Disorders, especially Myxoedema

by HENNING ANDERSEN, GUSTAV ASBOE-HANSEN, FLEMMING QUAADE and ROBERT WICHMANN

Queen Louise's Children's Hospital, Copenhagen, Denmark

Investigations of recent years have shown an increasing interest in the influence of hormones on the supporting tissues. A previous paper (ANDERSEN, ASBOE-HANSEN and QUAADE, 1953) dealt with the abnormal occurrence of hyaluronic acid and related substances in the skin of children with myxoedema. Several investigations (ASBOE-HANSEN, 1950) seem to show that such tissue changes may be due to an action of thyrotropin. The purpose of the present work was to investigate these conditions in children with endocrine disorders, especially myxoedema.

Biopsy of the skin: The technique used and the nature of the material have been previously described in detail (see also ASBOE-HANSEN, 1951). The following main features may just be summarized here:-

The specimen is removed with a skin biopsy drill (measuring 3 mm in diameter) from the olecranal region. It is fixed in a 4 per cent solution of basic lead acetate; the hyaluronic acid is then stained metachromically with methylene blue according to Lison's method. On the basis of the amount and distribution of the metachromic substances and the appearance of the mast cells, the fibrils and the epidermis, the following symbols were used in the histological diagnosis: + (severe myxoedema), (+) (slight myxoedema), and - (no signs of myxoedema).

Since the appearance of our first papers the material has been extended so that it now comprises 124 children. The composition of the material and the result of the skin biopsy are given in the following table which is shown at the exhibition:-

	Number	Skin biopsy positive + (+)	Skin biopsy negative
I. Unquestionable myxoedema	35	20	15
II. Obs. for myxoedema	22	10	12
III. No thyroid disorder	67	0	67
Total: 124			

Furthermore, the results of the skin biopsy in relation to thyroid medication in the children in Group I are shown at the exhibition.

Thyrotropin Assay

The thyrotropin content in the serum was determined according to a modification of a method elaborated by D'ANGELO and co-workers, who used tadpoles.

This test is based upon the fact that a period of hunger of even short duration will lead to atrophy of the thyroid gland at an early stage in the metamorphosis of the larva; the gland appears completely inactive, whilst at the same time the metamorphosis ceases. This interruption of the metamorphosis can be counteracted by the administration of thyrotropic hormone or thyroid hormone. In microscopical examinations of the thyroid gland it is possible to distinguish between the effects of these two hormones, as the changes produced in the height of the cells in the thyroid have proved to constitute a very sensitive biological test for the thyrotropic hormone.

Tadpoles of the African frog, *Xenopus laevis*, were used in the assays dealt with here.

The untreated serum samples were injected subcutaneously into the lower jaw of the subject, a single injection of 0.03 ml being given daily for 6 consecutive days. Forty-eight hours after the last injection the histological examination of the thyroid glands of the subjects was performed.

The degree of thyroid activity produced was determined according to a histio-quantitative method described by UOTILA and KANNAS for calculation of the percentage distribution of the various components in the thyroid gland, the proportion of epithelium, E %, being expressed in per cent of the total amount of epithelium, colloidal substance and stroma.

These calculations were made with 5 tadpoles in each assay.

A block diagram shows the values measured for E % after testing of sera from 12 children without a thyroid affection. Here, as in the other block diagrams, the full red line shows the average of all values of E % measured in the control series.

A measure of the thyrotropin content in sera from 10 children with unquestionable myxoedema, 4 children under observation for myxoedema, and 2 children with non-thyrotoxic diffuse struma is given in a similar block diagram by the values of E % measured in these cases.

Finally, the fluctuations in the thyrotropin content were studied in the same manner in 2 children with Graves' disease with pronounced exophthalmos from August (A) and September (S), 1953, respectively, to March (M) and April (A), 1954, respectively, both before and during treatment with methylthio-uracil and propylthio-uracil, respectively, plus iodine, and after subtotal thyroidectomy had been done.

Thyrotropin assay was made simultaneously with the skin biopsy in a number of children of Groups I, II and III. A table giving the correlation between the results of the two methods of investigation is shown at the exhibition. As a fourth group we include here the two patients with Graves' disease and one patient with juvenile struma.

The reasons why the skin biopsy was negative in barely half the number of children with clinically definite myxoedema have been previously discussed; it may just be pointed out here that a number of cases of myxoedema are undoubtedly "secondary", i.e. of pituitary determination owing to a decreased production of thyrotropin. If the changes in the skin described are due to an action of thyrotropin—and this is probable—we may thus expect to find a negative skin biopsy in children with myxoedema of pituitary determination. This view is supported by the last table: 6 out of the 9 patients of Group I had an increased content of thyrotropin in the blood combined with a positive skin biopsy; of the remaining 3 children, in whom the thyrotropin level was not increased and the skin biopsy was negative, 2 displayed signs of intracranial disease (deformity of the skull, convulsions; changes in the EEG or AEG). It may be mentioned that in all 3 cases the myxoedema had developed late and slowly.

The fact that both children with Graves' disease had a negative skin biopsy, whilst at the same time the thyrotropin content in the serum was increased (the specimens were removed in both cases at the beginning of the thio-uracil medication), is peculiar as compared to the correlation found in the patients with myxoedema. However, this finding has recurred in similar investigations in adult patients with Graves' disease, and cannot at present be explained in greater detail.

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Toxoplasmosis in a Child with Congenital Myxoedema

by HENNING ANDERSEN

Queen Louise's Children's Hospital, Copenhagen, Denmark

The case is reported to illustrate the difficulty in establishing clinically the diagnosis primary or secondary (pituitary) myxoedema and the value of skin biopsy and thyrotropin assay to the diagnosis.

A girl, born in 1953.

Past history of family and history of pregnancy: no special information.

Delivery normal, weight at birth, 3,100 g.

In the course of the first three months there was increasing psychic and somatic retardation.

At the age of 3 1/2 months she was of a typically myxoedematous appearance, but also presented microcephaly, chorioretinitis, intracranial calcifications and an abnormal EEG. As the toxoplasmosis reaction was positive in the dilution 1:1,250 in child and mother, the diagnosis congenital toxoplasmosis - pituitary myxoedema was established.

Skin biopsy first showed doubtful, later typical myxoedematous changes, and thyrotropin assay in the serum showed increased activity—both suggesting the presence of primary myxoedema. At the age of 4 months the patient died in collapse. Autopsy findings: *Athyrosis*—there were no traces of thyroid tissue anywhere; *cerebral toxoplasmosis* with severe inflammatory infiltrations with Toxoplasmae, *inter alia* in the hypothalamus and the pituitary.

The case was therefore considered one of primary myxoedema.

Cortisone in Diagnosis and Treatment of the Adrenogenital Syndrome

by HENNING ANDERSEN

Queen Louise's Children's Hospital, Copenhagen, Denmark

Records are shown of patients with adrenal cortex hyperplasia and tumor. The influence of cortisone on the excretion of 17-ketosteroids in the urine and on the development of the patients is illustrated.

Premature Pubarche¹

by E. THAMDRUP

By premature pubarche is understood precocious growth of sexual hair (pubes and axillary hair) without other symptoms of precocious puberty, i.e. without development of the genitals and, in girls, without growth of the breasts. Girls are not virilized as in the case of the adrenogenital syndrome.

The series of cases comprises 11 patients, 8 girls and 3 boys; the symptoms in the former were observed before the age of 8, in the latter before the age of 9 years. The patients were from Dronning Louises Børnehospital (children's hospital, Copenhagen), the Paediatric Department of the University Hospital, Copenhagen, and the homes for the mentally defective, Andersvaenge and Ebberødgaard.

The clinical symptoms and the results of examination of the patients

¹ Aided by a grant from King Christian X.'s Foundation.

are shown in a table. Six of the patients had severe cerebral disorders in the form of oligophrenia, epilepsy and, in 4 cases, spastic pareses. Three were blind, 2 had a coloboma of the uvea, and 4 had repeated periods of unaccountable rise of temperature (cerebral fever?). In 5 patients, air-encephalography revealed a considerable cerebral atrophy, also involving the hypothalamic region. Two boys were obese.

Hormone analyses of 24-hour urine showed a slightly increased excretion of 17-ketosteroids and corticoids in most cases. Oestrogenic hormon could not be demonstrated. In 2 patients, one analysis showed an excretion of gonadotrophin >50 M.U., in the other cases it was <50 M.U. Examination of vaginal epithelium stained according to Schorr's method showed infantile cells without oestrogenic influence. The genitals and the height of the patients corresponded to their chronologic ages, whereas the bone age was slightly accelerated in a number of cases. Roentgenologic examination of the pituitary fossa and of the urinary tract (adrenal regions) showed normal conditions.

In 1952 SILVERMAN *et al.* published a series comprising 29 patients (28 girls and 1 boy). The authors had observed a number of the patients until they arrived at the normal age of puberty. Development of the breasts and menarche occurred at the normal time, and none of the girls were virilized.

According to SILVERMAN *et al.*, the cause of the precocious growth of sexual hair may be (1) increased susceptibility of the hair follicles to androgenic hormone, and (2) increased secretion of adrenal androgens. The first explanation is purely theoretical, whereas both the work of SILVERMAN *et al.* and the present study seem to suggest a slightly increased production of adrenal cortical hormones.

Seven out of the 29 patients reported by SILVERMAN *et al.* were mentally retarded. The authors consider this to be a chance coincidence. In the present series of cases, 6 out of 11 children were deeply oligophrenic. In examinations of 139 children from 2 homes for mentally defective (99 boys <9 years and 40 girls <8 years) the writer found 4, all girls, with premature pubarche. This incidence is not found in a similar number of normal children. Air-encephalography in 5 children with premature pubarche showed diffuse cerebral atrophy which also involved the hypothalamic region. The precocious growth of sexual hair may possibly be explained as being caused by a disturbance in the cerebral regulation of the hormone production of the adrenal cortex, perhaps via the pituitary body.

The considerable preponderance of girls both in the series published by SILVERMAN *et al.* and in the present series may perhaps be explained by a possibly greater susceptibility of the hair follicles of girls to androgens.

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Testis Biopsy

by HENNING ANDERSEN, MOGENS ANDREASSEN and FLEMMING QUAADE

Queen Louise's Children's Hospital, Copenhagen, Denmark

The practical purpose of the work was to elucidate the question whether it will be permissible to postpone the operation for cryptorchism to the age towards puberty as is now the common practice in most countries.

In connection with orchidopexy, biopsy of 30 testes in all from boys at ages from 6 to 14 years was therefore performed. On the basis of the genital development and secondary sex markings the patients were classified as being in full puberty +; in early puberty (+), or not in puberty (0). Urines from a number of the patients were analysed for 17-ketosteroids and gonadotrophins. In the case of pre-operative treatment with chorionic gonadotrophin (physex) the time interval between the discontinuance of the therapy and the operation is given.

The biopsy technique is shown diagrammatically at the exhibition. The histological picture was evaluated on the basis of biopsies of normal testes, and classified according to Talbot as infantile, prepuberal and puberal.

None of the testes examined, whether retained or ectopic, were found to be definitely degenerated. The testes of patients treated with physex did not differ from those of the other boys.

To elucidate conditions after puberty, the results of 3 testis biopsies from 2 men, aged 17 and 35, (Surgical Clinic D, University Hospital, Copenhagen) are shown. In both cases a severe degeneration of the germinative epithelium was found, in the latter case there was severe peritubular fibrosis as well.

The four last cases differ from the others of this group, as the children, besides cryptorchism, had symptoms of diseases which might be supposed to influence the endocrine function: Encephalopathy with electro-encephalographic signs of hypothalamic lesion; genital aplasia; nanism with infantilism.

Changes of the Spine in Children with Myxoedema

by HENNING ANDERSEN

Queen Louise's Children's Hospital, Copenhagen, Denmark

There are rather few reports on roentgenologic changes of the spine in myxoedematous children. ROYER and MEGEVAND, 1954, have recently published an extensive survey of the subject, from which it appears that the series of SWOBODA, 1950, and EVANS, 1952, comprising 7 and 13 cases respectively, are the largest.

The change most frequently described is a defect in the upper part of L 2, or the adjoining vertebrae, often associated with kyphosis. Roentgenologically, this finding has been demonstrated as early as at the age of 9 months (EVANS). The deformity has been compared by several authors with similar findings in chondrodystrophy, Hurler's and Morquio's diseases.

In his text-book of 1945, CAFFEY drew attention to the fact that the myxoedematous spine is retarded, and he illustrated two cases, aged 3 and 8 years, presenting flattened vertebrae, large intervertebral spaces, persistent anterior vascular depression of foetal shape, and open neuro-central synchondrosis. BAMATTER, 1947, described the spine of a severely myxoedematous girl, aged 13, who presented platyspondylisis, wide intervertebral distance and increased distance between corresponding articular processes.

Writer's investigations.—Since January, 1953, X-rays have been regularly taken of the spines of myxoedematous children in the clinic. In a number of cases, previous X-rays were available for comparison. In estimating possible retardation, importance was attached to the above-mentioned findings which were compared with conditions in a number of normal children at the same ages, but of different build. As the variation in the normal development is greatest in the youngest children, and as the present series is so small, the degree of development was not estimated in these cases.

The examination comprised 14 children with unquestionable myxoedema, estimated according to the classic criteria, including the effect of thyroid extract.

The children were divided into two groups according to the intensity of the thyroid medication prior to the time when the first roentgenogram of the spine was taken:—

- (1) Cases 1–10, untreated or insufficiently treated.
- (2) Cases 11–14, satisfactorily treated.

Roentgenograms and a table giving the duration of treatment, the bone age and the degree of epiphyseal dysgenesis, compared with the findings in the spine, are shown at the exhibition.

Result of examination.

In the group of untreated or insufficiently treated children, spinal changes were found in all 10 cases.

Retarded development with platyspondylisis, wide intervertebral spaces and persistent anterior venous depression of foetal or infantile shape as the most constant and distinctive findings were demonstrated in all the children except two infants in whom, as already mentioned, conditions could not be estimated with certainty.

In two infants of this group, aged 3 1/2 and 4 1/2 months, changes were demonstrated in the corpora of the vertebrae; these changes were of the same appearance (condensation ring and, later, double contours) as those described by ENGESET, IMERSLUND and BLYSTAD in the case of the short bones of the extremities, and were present also in the ossification centres of the tarsus in these cases. Serial X-rays showed that the changes in the corpora and the tarsus appeared and disappeared at the same time in the course of treatment with thyroid extract.

Isolated defects in the lower thoracic or upper lumbar vertebrae were present in 4 cases.

In Case (2) the changes were demonstrated at a very early age (4 1/2 months). Case (3) has been observed for 6 years; in spite of intense treatment, the change can still be demonstrated. In Case (9) there was a bracket-like projection on the anterior surface of L 1 in addition to defects in TH 12.

In patients (9) and (10), absence of calcification of the borders of the vertebrae and abnormal structure of the corpora were also ascertained. These patients were brothers with myxoedema that had been diagnosed late; their case histories have been previously reported by ØSTER.

The cases of myxoedema that had been satisfactorily treated had normal spines, and the bones of their extremities were normal. The last two cases (13) and (14) were late-developed forms of myxoedema.

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Nutrition

Einwirkung verschiedener Faktoren auf die Dauer der Stillzeit

**Zusammengefasst an Hand von Erhebungen an der städtischen
Mütterberatungsstelle Stockholm**

von PER J. NORDENFELT

Das hier verarbeitete Material erfasst die Hälfte der 1950 an der Mütterberatungsstelle Stockholm eingeschriebenen Kinder, d. h. 4003 Fälle, von denen 3806 eheliche und 197 uneheliche.

39,0 % der Mütter hören mit Stillen auf, bevor das Kind 6 Monate alt ist, und 39,7 % konnten sechs Monate oder länger, ohne dauernde Zugabe anderer Nährmittel selbst stillen.

Ledige Mütter stillen ihre Kinder weniger lang als verheiratete.

8,6 % der Mütter gehen vor Ablauf von 6 Monaten beruflicher Arbeit ausser Hause nach, und zwar 37,1 % der Ledigen und 7,2 % der Verheirateten. Die Berufssarbeit verkürzt die Stillzeit um ein Beträchtliches.

Mütter unter 25 Jahren stillen am wenigsten lang; ältere, über 35 am längsten.

Je höher die soziale Schicht, der die Mütter angehören, desto länger die Stillzeit.

Allgemein wird das Erstgeborene am besten gestillt, die Folgenden ziemlich gleichmässig.

Kinder, die bei der Geburt weniger als 3000 g wogen, werden weniger lang gestillt als die anderen.

In engen Wohnverhältnissen (mehr als 2 Personen pro Wohnraum) lebende Mütter stillen etwas weniger lang, als solche die über mehr Raum verfügen.

Am genauesten sind die medizinischen Ursachen für eine verkürzte Stillzeit festzustellen; sie umfassen in vorliegendem Material 11,9 % Mütter und 3,4 % Kinder.

The Effect of Raw Certified Milk and Ordinary Pasteurized Milk on the Growth and Health of Two Uniform Groups of Infants

by HAAKON NATVIG and LARS GRAM

*Oslo City Board of Health, Department of Food-Inspection; The Institute of Hygiene,
University of Oslo; Åkeberg Nursery Home.*

By examination of two uniform groups of infants of which the one group had been fed on milk formulas made of raw certified milk and the

other group had been fed on milk formulas made of ordinary pasteurized milk the following results were obtained:

There was no difference in the increment of length or weight, no difference in the general condition, nutrition or dentition and no difference in the number of cases of alimentary anemia or dyspeptic conditions. The examination disclosed no significant difference between the two groups of children in the nature, frequency, course or duration of infectious diseases. The duration was calculated on the basis of the number of days with fever in proportion to the total days of stay in the nursery home.

By bacteriological and chemical examination of the milk it was found that both kinds of milk were of a high hygienic standard and there was no important difference in the bacteriological-chemical composition of the two brands of milk.

The article is to be published in *Acta Paediatrica Scandinavica*.

On the Incidence of Breast-feeding in Helsinki 1952

by NIILU HALLMAN, HEIKKI KALLIALA and LEENA TUUTERI

Children's Clinic, Helsinki

The material was collected with the help of the district nurses using questionnaires. It consists of 2,597 infants, i.e. nearly 50 per cent of all infants born in 1952 in Helsinki. Less than half of the infants were fed with breast milk at the age of 3 months and less than one-fifth at the age of 6 months. Compared with previous statistics from Helsinki the incidence of breast-feeding has decreased.

Such factors as the social position of the family, the age, the parity and the constitution of the mother and household help during pregnancy and lactation do not seem to have any certain influence in our material. The lactation period was somewhat shorter in the cases where the family lived in overcrowded conditions.

The cause of the early weaning was said to be illness of the mother or infant in one-fifth of the cases, and mother's occupation in one-tenth of the cases. In 50 per cent of the cases no cause could be given. The results suggest that the mother's attitude towards breast-feeding is more important than any other single factor.

Allergy

Age and Sex Variations of Cutaneous Reactions in Asthmatic Children

by E. WINGE FLENSBORG

Municipal Out-Patient Clinic for Allergic Diseases in Children, Copenhagen
(Physician-in-Charge: E. WINGE FLENSBORG)

Scratch tests with a considerable number of allergens (house dust [purified], feathers, various animal hairs, clothing textiles, foodstuffs, tree pollen, grass pollen, flower pollen and various moulds) were carried out in all children with the diagnosis of bronchial asthma and/or asthmatic bronchitis who have passed through the Clinic, viz. 853, of whom 573 boys (67 per cent) and 280 girls (33 per cent).

Only definitely urticarial, sharply and irregularly delimited immediate reactions were registered as positive.

Very considerable variations in the positivity of the cutaneous tests as regards age and sex were demonstrated.

For the great majority of allergens, the frequency of positive cutaneous tests increased with increasing age. The most marked increase was observed with house dust (from 1-2 per cent of the children in the two first years of life to 64 per cent of the children aged 12-15 years); feathers come next with an increase attaining 50 per cent in the age group 12-15 years.

A varying increase (from zero to a few per cent during the first years of life) was demonstrated in the various tests with animal hairs (cow hair up to 20 per cent, cat hair up to 18 per cent, horse dandruff up to 16 per cent, dog hair up to 11 per cent) with pollen (grass pollen up to 22 per cent, flower pollen [*compositae*] up to 18 per cent, tree pollen up to 13 per cent) and with moulds (up to 9 per cent).

As regards foodstuffs, conditions appear to be different, as when eggs were concerned, the frequency of positive cutaneous reactions decreased with increasing age (from approximately 7 per cent in the first two years of life to 4 per cent in the age group 3-5 years, 1 per cent in the age group 6-8 years and 3 per cent in the age group 9-15 years). Similar conditions were found when cow's milk was concerned while the frequency of the positive cutaneous reactions to fish appears to be constant through childhood.

Quite pronounced differences between boys and girls were observed in the cutaneous positivity. Boys react positively more frequently than do

girls and this holds true for all age groups and for the majority of the allergens. This is most marked when house dust and feathers are concerned.

From a purely practical point of view, the above findings indicate that it is insufficient to let asthmatic children undergo one single cutaneous testing only and subsequently base the treatment upon the result of this. Ideally, asthmatic children should be tested annually or at least as frequently as is indicated by possible unsatisfactory condition during treatment.

Provocation Experiments in Asthmatic Children

by K. DAMGAARD

*Municipal Out-Patient Clinic for Allergic Diseases in Children, Copenhagen
(Physician-in-Charge: E. WINGE FLENSBORG)*

As a positive cutaneous reaction indicates only that the patient is allergic but not that the allergen concerned is the causal agent of his symptoms, provocation experiments should be carried out as far as possible in order to attempt to separate the manifestly allergic patients from the latent allergic patients.

In the above Clinic, four types of provocation experiments are, as a rule, employed: (1) Natural exposure, (2) inhalation experiments, (3) the sniff test (nasal test), and (4) oral provocation with foodstuffs.

In the present paper, an account is given of the inhalation and sniff tests in 512 patients with asthma and/or asthmatic bronchitis with positive cutaneous reactions to one or several allergens. A total of 1,943 provocation experiments were carried out of which 1,163 were inhalation experiments and 770 were sniff tests. For technical reasons, only children under 3 years of age were examined.

Out of the 512 children, 62 per cent reacted positively on one or several provocation experiments with one or several allergens. With increasing age, a slightly increased inclination to react positively in the provocation experiments to one or several of those allergens, to which the child concerned showed a positive cutaneous reaction, was observed.

Out of the total number of 1,934 provocation experiments (one or several in each child), 43 per cent were positive. No definite age variation appears to exist in this connection.

More detailed analysis of the incidence of positive provocation experiments employing the most important allergens in various age groups does not reveal any typical tendency.

Great variation in the positivity of the separate allergens was noted (all

age groups taken together). Highest percentages of positive reactions were obtained by provocation with horse dandruff (73 per cent), grass pollen (54 per cent) house dust (52 per cent) and moulds (52 per cent).

This corresponds well to the clinical observation that these allergens may be regarded as particularly potent allergens with which pronounced positive cutaneous reactions are most frequently obtained and with which the frequency of general reactions during desensitization treatment is highest.

In 430 cases (in 254 children), sniff tests as well as inhalation tests were carried out with the same allergen in the same period. Among the positive provocation experiments, 39 per cent were positive in sniff as well as in inhalation experiments; 30 per cent were positive in inhalation experiments only and 31 per cent were positive in sniff tests only, i.e. both types of provocation experiment should be employed concurrently.

Good agreement exists between the information in the case-history concerning hypersensitivity towards an allergen and the result of the provocation experiment with the same allergen. When the case-history indicates allergy, 80 per cent of the provocation experiments were positive; when suspicion of allergy is aroused, 45 per cent were positive and when the case-history does not indicate allergy, 38 per cent were positive.

Similarly, an undoubted relation exists between the strength of the cutaneous reaction and the result of the provocation experiments. On scratch reaction (+) 24 per cent of the provocation experiments were positive; when the strength of the reaction was +, 38 per cent; ++, 53 per cent and +++, 60 per cent. This condition was found in all allergens examined.

The criteria for positive provocation experiments are shown in tables. It appears from these that the most powerful reaction, the asthmatic attack, is encountered virtually exclusively in patients with ++ and +++ scratch reactions.

The conceptions manifest and latent allergy to a certain allergen must not be interpreted as clearly separated conditions, for a number of different factors (other genuine allergic conditions, infectious allergy, mental and climatic conditions etc.) may determine whether the patient at the time of investigation reacts with clinical symptoms on exposure to the allergen.

The question whether the incidence of manifest allergy increases with increasing age cannot be answered with certainty by the present material; conditions may even vary with the various allergens.

Provocation experiments were repeated in 59 children at a 1-4-year interval with the same allergen once or several times. During this period, transition from latent to manifest allergy to one or several allergens probably took place in 22 of these children (37 per cent).

It is stressed that great care must be exerted in the conduct of provocation experiments. When a powerful general reaction might be anticipated, inhalation experiments are recommended in preference to sniff tests, as the dosage in inhalation is easier to graduate. Particular care should be exerted with patients with powerful cutaneous reactions to animal hair (in particular horse dandruff), pollen and moulds. Adrenaline should always be available.

Prematurity

Milk Drip Via an Indwelling Naso-gastric Tube in the Feeding of Premature Infants

by K. HOLMDAHL

Children's Clinic, Gothenburg, Sweden

Nourishment was administered to the premature infants via a rubber catheter (Nélaton No. 6) by a slow drip which continued during the greater part of the 24 hours. The calculated quantity of nourishment was divided into 3-4 portions. The tube was allowed to remain *in situ* in the same nostril for approximately 2 weeks after which it was changed to the other nostril.

Since 1952, this method was employed routinely when tube feeding was indicated and 72 premature infants are concerned to date. The total number of tube feeding days to date is 1,500. Some infants have been tube-fed until the age of 2-3 months.

The experience gained from the method which was demonstrated at the Exhibition in tabular form may be summarized as follows:

1. Vomiting and attacks of cyanosis occur despite this form of tube feeding. Vomiting is, however, not so frequent. Aspiration occurred undoubtedly in a couple of cases.

2. Apart from increased secretion of mucus and some swelling of the nasal mucosa in a number of cases, no local complications from the mucous membranes occurred which could be attributed to the nasal tube.

3. The mortality among the premature infants has fallen considerably. The improved results in the lowest weight group are particularly noteworthy. Since 1952, 5 infants with birth weights under 1,000 g (2 lbs. 3 oz.) have survived as compared with only 2 surviving infants in the period from the opening of the Department in 1940 until 1952. The mortality after survival for the first 48 hours has fallen more than has the mortality during the first 2 days of life. The difference is, however, not significant.

here and even if it were, no conclusion can be drawn from this as regards the value of tube feeding. Other changes in the care of premature infants have been instituted during the same period.

4. The method has other advantages. The administration of nourishment can be instituted earlier and greater quantities of nourishment be supplied. Handling of the infant is reduced. When oxygen therapy in an incubator is employed, the bottles of the drip apparatus may be replaced outside the incubator so that the concentration of oxygen may be maintained more constant. Time is saved in feeding the infant and this method of feeding may be carried out by less trained personnel.

Retrorenal Fibroplasia in Premature Infants and Its Relation to Oxygen Therapy

Illustrated by a Material From a Danish Premature Ward

by P. BRÆNDSTRUP and E. WINGE FLENSBORG

Children's Hospital, Martinsvej, Copenhagen, Denmark
(Physician-in-Charge: E. WINGE FLENSBORG)

Since July 1950, systematic ophthalmoscopic examinations in view of the incidence of retrorenal fibroplasia (r.f.) were undertaken. Originally only premature infants with birth weights under 1,500 g were examined while later this examination was carried out in all premature infants with birth weights under 2,000 g. The frequency of examinations has been increasing.

A total of 204 premature infants were examined with the following distribution as regards weight groups:

$\leq 1,000$ g (2 lbs. 3 oz.),	3 infants
1,001-1,500 g (2 lbs. 3 oz.-3 lbs. 5 oz.),	78 infants
1,501-2,000 g (3 lbs. 5 oz.-4 lbs. 7 oz.),	123 infants

From two tables in which the results of the total number of ophthalmoscopic examinations and the relation to oxygen therapy were registered the following appears:

1) 81 premature infants with birth weights $\leq 2,000$ g received no oxygen therapy whatsoever. All ophthalmoscopic examinations (195) carried out in these infants showed normal conditions.

2) 42 premature infants with birth weights $\leq 2,000$ g received oxygen therapy for 1-4 days. All ophthalmoscopic examinations (127) of these infants showed normal conditions.

3) 76 premature infants with birth weights $\leq 2,000$ g received oxygen therapy for 5 days or more (maximal individual duration of treatment with oxygen was 63 days). *Varying degrees of retrorenal fibroplasia were demonstrated in 26 of these infants. In 14 of these cases the condition was reversible, while in 12 it was irreversible.*

Expressed as histogram, the relation between the incidence of r.f. and the duration of oxygen therapy is demonstrated in greater detail. Among other things, it appears from this that:

4) Among 59 premature infants $\leq 2,000$ g who received oxygen therapy for 5–29 days, irreversible r.f. developed in 6 (10 %)

5) Among 17 premature infants $\leq 2,000$ g who underwent oxygen therapy for more than 30 days, irreversible r.f. developed in 6 (35 %).

A more detailed analysis of the onset of r.f. in the present material shows:

6) Changes due to r.f. do not occur during oxygen therapy when this is carried out continuously nor during the initial phase of intermittent oxygen therapy.

7) r.f. is frequently demonstrated immediately after discontinuation of oxygen therapy.

8) Relation may exist between the duration of oxygen therapy and the onset-time of r.f. (in relation to the discontinuation of the oxygen therapy): the shorter the duration of oxygen therapy, the later the onset of r.f. changes.

9) In the present material, r.f. did not develop later than on the 27th day after discontinuation of oxygen therapy.

Demonstration of all slighter, reversible cases of r.f. require very frequent examinations as they frequently are of very short duration. The present material is therefore suitable for analysis of the irreversible cases only.

Such an analysis was carried out in relation both to the duration of oxygen therapy and the degree of prematurity (birth weight) and revealed:

10) Among 36 premature infants with birth weights $\leq 1,500$ g who received oxygen therapy during 0–15 days, none developed irreversible r.f.

11) Among 31 premature infants with birth weights $\leq 1,500$ g who received oxygen therapy during 15–63 days, 8 developed irreversible r.f. and of these 5 became blind.

This appears to indicate that the duration of oxygen therapy rather than the degree of prematurity is decisive in the development of r.f.

Until January 1952, all premature infants with birth weights under 2,000 g were treated liberally with oxygen until a weight of 2,000 g was attained. During this period, 71 premature infants were examined in whom 13 cases of r.f. were demonstrated, 5 of which were irreversible.

For a short period, every alternate premature infant was treated with oxygen but since June 1, 1952, oxygen has been administered in this Department only in emergencies and during this period only 2 mild (reversible) cases of r.f. were demonstrated among 82 premature infants.

During the same period (1952-54), 66 premature infants admitted to the Department from elsewhere had been treated with a reduced oxygen régime with stepping down of the oxygen percentage. Ten of these infants developed r.f. and out of these, 6 were irreversible.

12) It appears from the above, that a drastic reduction in the employment of oxygen in a department for premature infants, so that oxygen is administered only in emergencies and for as short a period as possible, reduces the incidence of r.f. considerably whereas a moderate reduction in the oxygen therapy even when this is terminated by stepping down of the oxygen percentage does not involve any demonstrable decrease in the incidence of r.f.

13) We are of opinion that no direct toxic effect of the oxygen comes into consideration as still active cases of r.f. were «treated» with oxygen in this Department as well as elsewhere whereby the changes in a number of cases regressed.

14) The mortality among premature infants with birth weights 1,001-1,500 g admitted to this Department during the first 24 hours of life was as follows: During the period of liberal oxygen administration, 32 per cent. During the period of oxygen administration in emergencies only, 33 per cent.

Conclusion

Retrorenal fibroplasia is an artificial condition which develops in premature infants as a retinal reaction following oxygen administration (relative anoxaemia).

Oxygen should be administered to premature infants in emergencies only and for as short a period as possible.

Prevention of Retrorenal Fibroplasia

by HILDA BLIX

Children's Clinic, Gothenburg, Sweden

Since November 1950 all premature babies in Gothenburg have had a funduscopic examination once a week until discharge. After that they were kept under control until the age of 6 months. During the first year

4 premature babies had early retrorenal fibroplasia changes. We tried vitamin E and ACTH without success. The changes advanced to a cicatricial stage.

Since July 1952 we have tried to prevent retrorenal fibroplasia according to Szewczyk, by giving oxygen in as low a concentration as possible and for as short a time as possible. We also have weaned the babies from oxygen gradually before it was withdrawn. During this time 59 children with birth weights less than 1,750 g were discharged. None of them had retrorenal fibroplasia at the age of 6 months.

In earlier years (1946 until June 1952) premature babies had been treated with oxygen in incubators, often for a long time and at high concentration before the oxygen was suddenly withdrawn. Among the 199 children with birth weights less than 1,750 g so treated, 12 had retrorenal fibroplasia in a cicatricial stage. Among 34 children with birth weights less than 1,350 g, 7 had the disease. All children with retrorenal fibroplasia have got oxygen in incubators for more than 3 weeks. Seven of them had at least one funduscopic examination in the newborn period and all had normal fundi while under oxygen. The 4 latest cases were followed with funduscopic examination for at least two months. These children had wide and tortuous retinal vessels for the first time 1-2 weeks after oxygen had been withdrawn. In spite of the restricted oxygen administration during the last years, one child with a birth weight of 2,420 g came for control 5 weeks old with fully developed retrorenal fibroplasia. This child had never been given oxygen and was discharged with normal fundi one week old. After that the child had a respiratory infection.

According to Szewczyk, retrorenal fibroplasia is anoxic in character, either because of a sudden withdrawal of oxygen at high concentration or as a result of respiratory infection or general disease which suddenly interferes with the oxygenation. Our experience supports this theory. It seems to be possible to prevent retrorenal fibroplasia due to oxygen administration, but it has not been possible to prevent cases due to a disease which suddenly makes the child asphyctic.

A Follow-up Examination of Small Premature Infants at School Age

by H. BLIX and K. HOLMDAHL

Children's Clinic, Gothenburg, Sweden

Seventy-four children with birth weights less than 1,750 g (4 lbs. 2 oz.) who had been hospitalized in the Department for Premature Infants in

Gothenburg during the years 1940–46 and all of whom had attained the official school age (the calendar year in which the child attains 7 years) were examined in view of scholastic attainments and physical development. If the children had siblings, the scholastic attainments were compared with theirs, premature siblings being excluded. Among the premature children, 41 had siblings.

The result of the investigation, which was demonstrated in tabular form, may be summarized as follows:

1. Children, born prematurely, experience greater difficulty in school than do their contemporaries and this takes the form of postponement of school attendance, failure to advance to the next class or the necessity of attending special classes on account of mental retardation. The difference is statistically significant for the entire group as well as for the group with birth weights 1,510–1,750 g (3 lbs. 5 oz.–4 lbs. 2 oz.).
2. Children born prematurely require education in institutions for mental defectives or in schools for educationally retarded children to a greater extent than do their siblings. The difference is significant for the entire group and probable for the group with birth weights 1,510–1,750 g.
3. The school reports in the academic subjects are somewhat poorer when children are born prematurely and attend the normal classes in primary schools but this difference may be random. For physical culture, conduct and discipline, the reports were approximately the same.
4. No difference could be demonstrated as regards weight and height.
5. Out of the 33 children, born prematurely, who had no siblings, 13 experienced difficulties at school in the forms mentioned above.
6. Out of the 5 children who suffered from severe attacks of cyanosis or in whom considerable feeding difficulties were experienced while in the Department for Premature Infants, 3 attended classes for educationally retarded or for educationally subnormal children.

Cardiovascular System

The Heart and Circulation in Funnel Chest

by Å. GYLLENSWÄRD and H. LODIN

Dept. of Pediatrics and Radiology, Academic Hospital, Uppsala, Sweden

A marked degree of funnel chest produces pressure on the heart, which is partly compensated by rotation and sinistro-position. The series of pressure curves and angiograms presented shows that in many cases

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here exists however considerable deformity of the right ventricle and pulmonary artery in particular, with simultaneous increase in pressure in the pulmonary circulation. After operation the heart and pulmonary circulation are normalized. The authors are of the opinion that investigations of this type make it possible to select those cases of funnel chest which apart from cosmetic considerations, require surgical correction.

Haemangioma in Premature and Full-time Newly Born Infants

by K. HOLMDAHL

Children's Clinic, Gothenburg, Sweden

The term haemangioma as employed in the present paper, indicates hypertrophic endothelial haemangioma. Such tumours are situated superficially and grow more rapidly than does the surrounding tissue. As a result, they become more or less raised above the skin surface and therefore assume the characteristic strawberry-like appearance.

Capillary haemangioma (so-called telangiectases) and the more deeply situated cavernous haemangioma are thus not included in the investigation.

The primary material consists of 293 premature infants with birth weights of under 2,000 g (4 lbs. 7 oz.), 347 premature infants with birth weights between 2,010 and 2,500 g (4 lbs. 7 oz.-5 lbs. 8 oz) and 186 full-time infants. In the majority of cases, these infants were examined regularly for the occurrence of haemangioma until the age of 6 months. In a number of cases, the period of observation was even longer.

The result, which was demonstrated at the Exhibition in tabular form, may be summarized as follows:

1. The tendency to formation of haemangioma seems to be equal all over the skin surface.
2. Haemangioma are very rare at birth and develop, as a rule, during the second to fourth week of life.
3. The risk of developing haemangioma is perhaps somewhat greater in the smallest premature infants during the first three weeks of life but the difference is not significant.
4. The final risk of developing haemangioma is the same both for premature and for full-time infants (approximately 12-13 per cent at the age of 6 months).
5. On account of this tendency to proliferation in the vascular system, which is most pronounced during the second to fourth week of life, as ex-

pressed by haemangioma, these demand interest from more than a cosmetic point of view: they constitute an interesting biological problem.

6. As haemangioma are as common in full-time infants as in premature infants in the various weight groups, one of the arguments for a connection between haemangioma and retrosternal fibroplasia is excluded.

7. Haemangioma show a spontaneous tendency to regress during the second six-month period of life.

Infections

Results of 181 Tuberculous Meningitis Cases, Treated in 1949-1954

by OLE WASZ-HÖCKERT

Childrens Clinic, Helsinki, Finland

181 cases of tuberculous meningitis, 47 of them with miliary TB and meningitis, are reported. Cases treated more than 2 months in other hospitals are not included in this material.

Table 1
Methods of treatment

Treatment groups	SM		PAS perorally g/kg/day	Isoniazid		Cortisone	
	Dihydro-streptomycin sulfate intramus., mg/kg/day	Streptomycin sulfate intrathecal		Tabl. perorally mg/kg/day	Solution intrathecal mg/kg/day	Tabl. perorally mg/kg	Hydrocortisone solutions intrathecal mg/kg
I	100-50	25 mg i.lumb.	—	—	—	—	—
II	50-25	1-3 mg/kg ¹	0.3	—	—	—	—
III	30-20	— ²	— ²	5	0.5	—	—
IV	20-10	— ³	— ³	10	— ³	2	1

¹ 1 mg/kg for 7-15 year olds
² — — — 3-6 — — half these doses were given in suboccipital and intraventricular injections
³ — — — 0-2 — —

20 of the children were 0-1 year of age, 64 between 1-2 years. Only 12 patients came in the 10-15 year age group.

Table 2
Results of treatment

Treatment group	Cases	Recovered	Died	Time of treatment (mean)	Time of after-observation (mean)
I	17	5	12 (70 %)	8 months	4 years
II	103	53	50 (48 %)	6 $\frac{1}{2}$ "	3.2 "
III	37	26	11 (29 %)	6 "	1.6 "
IV	24	20	4 (15 %)	5 "	5 months

It must be noted that the patients come to the Children's Clinic from all over the country (up to 950 km), and this is a reason why cases are often admitted too late. Thus 7 children died within 72 hours and a further 31, 0-13 days after admission. If these 31 essentially hopeless cases were excluded from the material, the death rate would be 30.6 per cent. It should also be mentioned that all the cases are of human strains. Bovine TB does not exist in Finland.

Complications: Relapses 4, deafness 12 and hardness of hearing 4 cases. The high blockage in the CSF-system is the most dangerous complication. Every known method of treating high blocks has been used (streptokinase, over-compression, PPD, tryptar), but trepanning and ventricular drainage with permanent catheter still seems to be the best method (8 out of 40 trepanned cases recovered). Hydrocortisone intrathecally seems to prevent the onset of high-blockages. (See also: WASZ-HÖCKERT: Nord. med. 51: 101, 1954.)

Are Children Not in the Care of Their Mothers More Susceptible to Acute Infectious Illnesses than Children who are in the Care of Their Mothers?

by RUTH WEGELIUS and MIRJAM LINKOMIES

Pediatric Dept., Maria Hospital, Helsinki, Finland

Among 511 children who during the months of January and February 1954 were examined in the Out-patient Ward of the Ped. Dpt. of Maria

Hospital, Helsingfors, no difference was observed in the frequency of acute infectious illnesses in children who went to Kindergartens and similar institutions and children who stayed at home with their mothers.

Interstitial Plasma Cell Pneumonia

by E. K. AHVENAINEN, N. HALLMAN, P-E. HEIKEL, HILKKA TÄHKÄ,
ANNELI YLINEN and ARVO YLPPÖ

Children's Clinic, Helsinki, Finland

About 200 cases of interstitial plasma cell pneumonia have been treated at the Children's Clinic of the University of Helsinki and at the Children's Castle in 1949-52. Most of these patients are premature babies or infants recovering from a serious disease. About 30 of them are full-term infants who have been treated in an institution, because of their mothers' active pulmonary tuberculosis.

The typical picture of the disease shows lack of appetite, arrested gain in weight, rapid and difficult breathing. The temperature was, however, usually normal. In the blood, erythrocytes and reticulocytes often increase as well as plasma calcium and non-protein nitrogen. In urine there is often protein and the urinary sediment reveals leucocytes, erythrocytes, epithelial cells and sometimes granular or hyaline casts. All these symptoms return to normal during the recovery which takes some weeks. The mortality was in this material in the first years about 60 per cent and later on about 20 per cent.

47 patients have been examined 1 1/2-5 years after the disease. Four of them have a continuously high plasma calcium and non-protein nitrogen, and are mentally and physically retarded. Their skulls and skeletal bones show osteosclerosis.

An autopsy was performed on all the patients who died in the acute phase of the disease. The lungs showed grossly and microscopically interstitial plasma-cell pneumonia and the kidneys revealed signs of "lower nephron nephrosis" and calcium crystals.

Rubella During Pregnancy

by ROLF LUNDSTRÖM

Kronprinsessan Lovisa's Children's Hospital, Stockholm, Sweden

The Poliomyelitis Epidemic of 1953 in Stockholm and the Rest of Sweden

Management of Poliomyelitis Cases and Technical Equipment Required

by JUSTUS STRÖM and ELIAS BENGTSSON

Infectious Diseases Hospital, Stockholm, Sweden

The organization of the National Poliomyelitis Association of Sweden and of an infectious diseases hospital is schematically described, with special reference to the use of respirators in acute cases.

The epidemic of 1953 is shown in figures and tables: seasonal variation, geographical distribution, age and sex incidence of different paralytic forms, therapeutic results in severe cases, mortality in various forms of artificial respiration, etc. One noteworthy finding is that the incidence of paralysis shows a maximum between the ages of 20 and 35, and that the relative incidence of severe cases with respiratory and pharyngeal paralysis continues to rise steeply in males, but not in females, after that age. The importance of larger units at the treatment centers is illustrated by the fact that the major centers had a substantially lower mortality than the small units in the provinces.

A tabulation is presented of the technical equipment required in a department for acute respiratory cases, together with a description of wards and nursing departments, and a formulation of the desiderata as to the capacity of different laboratories. Figures and data are given showing the design and principles of the different types of respirators in use in Sweden today.

Neurology

The Normal Electroencephalogram in Infants and Small Children

by STEN BILLE and SVEN BRANDT

Queen Louise's Children's Hospital, EEG Unit, Copenhagen, Denmark

The normal material has been collected from over 100 healthy children, 0 to 6 years of age, without known cases of epilepsy in their families and who themselves have never suffered severe head injuries or had seizures of any kind.

Part of the exhibition should offer a practical solution to the question: "How to get a quick and still safe impression of the dominant frequency in a child's waking record?" For this purpose 10 seconds' cut-outs have been taken from 10 different children within each age group. These 10 cut-outs have been arranged underneath each other on cartoons, that can be folded together as a book. The following age groups have been used: 0-3, 4-6, 7-12, 13-18, 19-24 months. Further: 2-2 1/2, 2 1/2-3, 3-4, 4-5 and 5-6 years.

For each age group two folding books have been made, named A and B. In A are demonstrated typical average dominant rhythms. For B the most extreme variations from the average frequency in respect to potentials of longer durations have been chosen, mostly from periods of definite waking phase, sometimes from periods questionable of slight drowsiness.

The EEG of a child to be examined can quickly be compared with models from the corresponding age group. The method offers information not alone about the variation among different children of each age group but also—by comparing A and B models—about the occasional individual fluctuations found under normal circumstances.

Another part of the exhibition demonstrated EEG-changes during drowsiness and sleep which may be mistaken for specific epileptic abnormalities.

Among 136 healthy children four showed EEG patterns which had to be classified as definitely abnormal (about 3 per cent).

Electroencephalographic Findings in Children with Febrile Convulsions

by RAGNHILD BJERGLUND and SVEN BRANDT

Queen Louise's Children's Hospital, Seizure Unit, Copenhagen, Denmark

An abnormal EEG was found in 25 per cent of 129 children with one or more epileptic seizures exclusively in relation to temperature rise. Abnormalities were most frequent in females and among children aged 3-4 years. The frequency was highest in the group with more than one seizure, slightly higher following seizures of long duration than after seizures of short duration. Not higher in children examined shortly after the attack compared with those examined after a longer interval. Abnormalities may disappear with time, may persist unchanged or may exaggerate. A few children with normal EEG from the start may show abnormalities after later seizures.

EEG findings indicate that "febrile convulsions" are actually epileptic seizures although for the most part caused by a mild form of epilepsy with a fairly good prognosis. On the other side, not a few adult patients with persistent epilepsy had their first epileptic manifestations in early childhood as febrile convulsions. EEG offers a better chance to screen such cases for early and sufficient antiepileptic treatment.

Some Figures to Throw Light on Aetiological Factors in a Cerebral Palsy Material of Altogether 320 Patients

by MARIT SKATVEDT

Children's Hospital, Rikshospitalet, Oslo

1. Weight at birth known in 266 cases

Among 94 patients with bilateral spastic paresis 50 per cent had a birth-weight under 2,500 g. In the rest of the material 16 per cent weighed under 2,500 g and 16.2 per cent over 4,000 g. If the patients weighing under 3,000 g are ignored, 26.9 per cent of the patients weighed over 4,000 g. (In a normal material consisting of 2,060 infants, the corresponding percentage was 17.9.)

2. The course of delivery in 301 cases

59 per cent were stated to be normal, 41 per cent to be pathological. In the ataxia group 9 out of 16 patients had a pathological delivery, and this was so in 48 per cent of the cases of hemiparesis, in 45 per cent of the cases in the mixed group, in 34 per cent of the cases of bilateral spastic paresis, and in 35 per cent of the cases of athetosis. It is remarkable that as many as 41 per cent of the pathological deliveries belonged to the prolonged delivery group.

3. Postnatal aetiological factors

Here asphyxia and signs of injury to the brain during or just after delivery hold a dominating position, being present in as great a proportion as 48 per cent. Kernicterus with Rh incompatibility was found in 4.9 per cent, whereas 4.2 per cent had prolonged and severe jaundice without Rh incompatibility. In 10.5 per cent there was no demonstrable prenatal, natal or postnatal cause.

On Seasonal Variation in the Galvanic Excitability of Infants in Finland

by ANNikki SEPPÄ-KIVALO

Children's Clinic, Helsinki, Finland

The galvanic excitability of healthy infants, 1 to 12 months old, from a well-baby clinic was determined during one year. A series of 236 galvanic excitability tests made on 158 infants displayed a seasonal variation of galvanic excitability, the sensitivity to galvanic current being highest in the summer and lowest in the winter. It was found that a distinct relation exists between galvanic excitability and ultraviolet radiation of the sun.

As factors connected with galvanic excitability, the plasma total calcium, inorganic phosphorus, and total protein were determined in 90 healthy infants (271 calcium and protein determinations, 210 phosphorus determinations). The ionized calcium fraction was computed from total calcium and total protein. Ionized calcium fraction and inorganic phosphorus were highest in the spring and summer and lowest in the autumn and winter.

The seasonal changes in galvanic excitability cannot be explained by the changes in the ionized calcium fraction. An explanation by means of the changes in phosphorus is possible.

The Cerebral Palsy Treatment Unit at Kronprinsessan Lovisa's Barnsjukhus, Stockholm

by K.-M. HERRLIN

Crown-Princess Lovisa's Children's Hospital, Stockholm, Sweden

Kronprinsessan Lovisa's Barnsjukhus is now a treatment centre for cerebral palsied children in Stockholm. The major part of the work is carried out at the medical and psychiatric clinics, with their diagnostic and therapeutic resources of various kinds. Every neurological case of the cerebral palsy type is examined and evaluated by the hospital team (paediatrician, neurologist, orthopaedic surgeon, physiotherapist and social worker) and by one of the child psychiatrists. Other specialists are consulted if necessary. The appropriate treatment is then planned. The team continues to supervise the patient at a special out-patient department. This permanent unit, with specialists in the various fields, has been gradually enlarged

since the autumn of 1951. Such a unit is essential if as all-round an evaluation as possible and planning of therapy on this basis are to be realized.

The diagnosis of cerebral palsy is a neurological diagnosis. It is not infrequently difficult to establish, and requires great experience. This applies, for example, to the evaluation of aetiological factors and to the appraisal of the neurological symptoms and the mental development. Of the children brought to our hospital by their parents, or referred by other physicians as cases of cerebral palsy, no less than 16 per cent (23/143) were found to suffer from other developmental disturbances or neurological disorders, in two cases a brain tumour. These figures apply to the period November 1951 to April 1954.

The cause of the brain damage in the 120 children with cerebral palsy (77 boys and 43 girls, aged 0–16 years) was considered to be pre-natal in 23 per cent, natal in 41 per cent, post-natal in 19 per cent and of unknown origin in 17 per cent. It may also be mentioned that 22 per cent were prematurely born (birth weight less than 2,500 g) and 7.5 per cent were twin births.

The patients were classified according to the mental development into normal (40 per cent), mentally retarded but educable (49 per cent) and uneducable (11 per cent). A classification according to the main symptom from the therapeutic view-point gave the following figures: spasticity as the only or predominating symptom, 59 per cent; spasticity and marked extrapyramidal and/or cerebellar symptoms, 18 per cent; no spasticity (athetosis, rigidity, ataxia, atonia or mixed forms), 23 per cent. Among the other prominent symptoms was epilepsy; it was present in 15 per cent of the mentally normal children, in 24 per cent of the mentally retarded and in 38 per cent of the uneducable. Disturbances in the function of the eye muscles were found in 40 per cent of the whole series.

The main form of therapy has consisted of sets of exercises of muscular movements, adapted to the individual case and started as early as possible. Other forms of therapy, e.g. orthopaedic surgery or applicances, speech therapy, and the choice of suitable institutional care or schooling, have also been individualized as far as possible. The cerebral palsied child has consistently been regarded as a whole, and the psychological and humanitarian side of treatment has been considered to be of at least as great importance as more specialized forms of therapy.

Air-encephalographic Findings in Cerebral Palsy

by SIGURD EEK

Radiological Department, Children's Hospital, Rikshospitalet, Oslo

Among 320 patients in a cerebral palsy material, 85 were subjected to an air-encephalographic examination (LEG). Among them were 27 examinations which were discarded as incomplete or unsuccessful. Among the 58 successful examinations there were 10 showing a normal ventricular system. The remaining 48 were definitely pathological. The 10-to-48 ratio of normal to pathological LEG's is presumably not representative for the whole of the material, for it was usually the worst cases which were examined. A selection of encephalograms, representing various clinical types of cerebral palsy (right- and left-sided hemipareses, bilateral spastic pareses, athetosis and mixed forms) is demonstrated. Representative Röntgenograms of cases of pure ataxia are lacking.

The 58 cases showing a successful LEG are classified according to type in the following way:

	Normal LEG	Pathological LEG	Total
Hemiparesis			
Right-sided	1	5	6
Left-sided		3	3
Bilateral spastic paresis	6	19	25
Athetosis	2	2	4
Ataxia		1	1
Mixed form	1	18	19
	10	48	58

Among the 48 patients with a pathological LEG was one with right-sided hemiparesis and signs of local cortical damage as the only finding. All the other 47 patients showed diffuse, central damage—general dilatation of the lateral ventricles, dilatation of the third and/or fourth ventricle and large basal cisterns. The dilatation of the third ventricle was by far the most common finding. Several of the patients also showed at the same time radiological manifestations of cortical damage, either diffuse or, in the case of the hemipareses, local. If a comparison is made of the LEG and EEG findings in the 58 cases with successful LEG, the present material shows better agreement between the air-encephalographic and clinical examinations than between the electro-encephalographic and clinical examinations. Among the above-mentioned 58 patients 39 were subjected

to EEG examinations. It was particularly in the group of bilateral spastic paresis cases that the findings were most at variance; among the 19 patients showing a definitely pathological LEG there were 17 given an EEG examination, and among them were 8 showing normal electro-encephalographic conditions.

Röntgenological Conclusions

1. With only one exception, all the 48 cerebral palsy patients with pathological air-encephalographic findings showed damage to the central cerebral structures irrespective of the clinical type.
2. A particularly common finding is a pathological dilatation of the third ventricle (more than 8 mm wide) indicating damage to the nuclei and/or nerve fibre tracts in the area of the basal ganglia. The radiological evidence cannot decide which structures are involved.
3. In 8 of the 9 cases of hemiparesis examined, pathological changes, to some extent considerable, were found on the side corresponding to the clinical lesion. But in 7 of these 8 cases there were other changes of a more general character without any corresponding clinical finding.
4. Cases of bilateral spastic paresis, pure athetosis, pure ataxia or mixed forms present nearly always the same radiological picture. Patients presenting marked spasticity often show considerable dilatation of the fourth ventricle.
5. In some cases congenital malformations such as agenesis corporis callosum, septum pellucidum cysts, etc. were found. In other cases it was, however, not possible to decide on the radiological evidence whether the cause of the pathological findings was a congenital malformation or damage inflicted before, during or after birth. It will therefore often not be possible to decide by radiological means whether a cerebral *atrophy* exists.
6. LEG may be normal in patients with slight clinical symptoms. This is very often the case in the group of bilateral spastic pareses.
7. In the present material the air-encephalographic examinations were superior to the electro-encephalographic examinations with regard to the demonstration of pathological changes in the cerebrum.

Blood

The Osmotic and Mechanical Resistance of the Red Blood Cells of Foetus and Child

by STIG SJÖLIN

The Children's Hospital, the Academic Hospital, Uppsala, Sweden

The osmotic resistance of the red blood cells shows certain characteristic changes during foetal life and childhood. This resistance is considerably lower in the young foetus than in the blood in the umbilical cord of a full-grown infant. On the other hand, this resistance is practically the same in the older foetus as it is in the blood of the umbilical cord. The blood in the umbilical cord and during childhood shows an increase of the number of resistant red cells in comparison with adults. The variations in osmotic resistance can at any rate to some extent depend on a form factor. These variations may be taken to depend on differences in the composition of the red blood cell population or on differences in the red blood cells in an *in vivo* environment. *The mechanical resistance* of the red blood cells is reduced during the first two or three months of life and under different haemolytic morbid conditions (congenital haemolytic anaemia, acquired haemolytic anaemia, erythroblastosis).

The Water- and Ion-Permeability of the Foetal Red Blood Cells

by STIG SJÖLIN

The Children's Hospital, Academic Hospital, Uppsala, Sweden

The red blood cells of the umbilical cord show a lower permeability for water than the red blood cells of adults. The red blood cells of the umbilical cord lose potassium and take up sodium more quickly when stored at a low temperature (+4° C) than do the red blood cells of adults. These differences of permeability are interpreted as indicating membrane qualities which vary in the two types of cells.

Investigations of the Blood of the Umbilical Cord

by URBAN FURUHJELM, IRJA SALMI and KALLE ÖSTERLUND

Children's Hospital, Helsingfors, Finland

This investigation concerns analyses of the arterial and venous blood of the umbilical cord and of the venous blood of the mother. The content of

the following substances in the plasma was determined: Calcium, magnesium, potassium, sodium (K and Na also intracellular), proteins, alkali reserve, chlorides (also intracellular) proteins, alkali reserve, chlorides (also intracellular) and non-organic phosphorus. The blood sugar and total fat in the serum was also investigated.

It was found that the Ca content was always higher in the umbilical vein than in the umbilical artery, whereas the K and Na content was evidently the same in arterial and venous blood. The protein figures were somewhat higher in the arterial blood than in the venous blood of the umbilical cord. A "chloride-shift" was observed in the case of Cl. The alkali reserve was remarkably low in the mother, whereas the figures for umbilical cord blood were somewhat higher, although definitely lower than the normal in the new-born. The sugar content of the blood of the umbilical vein was always higher than of the umbilical artery (in some cases the figures were the same), and there was a positive correlation with the figures for the mother. The total fat was sometimes higher in the artery, sometimes in the vein. The means were of the same size, and there was a positive correlation with the mother's blood.

Roentgenological Findings in the Bone System of Leukaemic Children

by PER-ERIK HEIKEL and RUTH WEGELIUS

Children's Clinic, Helsinki, Finland

Changes in the long bones were found in 72 of 93 children suffering from leukaemia. In some of the cases the changes appeared before any pathological findings were observed in the bone marrow and the peripheral blood. The changes consisted mainly of zones of metaphyseal decalcification and periosteal reactions. Osteolysis and osteosclerosis were also found.

Treatment of the Anaemia of Praematurity with Cobalt

by RUTH WEGELIUS

Childrens Ward, Maria Hospital, Helsingfors, Finland

0.30 mg cobalt was given daily i.m. during a 10-day period to premature babies suffering from anaemia. An increase of the reticulocyte count, the haemoglobin value and the erythrocyte count were observed during the

treatment. 5 mg cobalt chloride given per os every other day after the intramuscular treatment did not cause any further increase of the Hb and the red blood cells.

Exchange Transfusion in the Haemolytic Disease of the Newborn

by H. R. NEVANLINNA

Children's Clinic, University, Helsinki, Finland

The technique and results of exchange transfusion in 120 cases of haemolytic disease of the newborn due to maternal Rh immunization with a mortality rate less than 10 per cent are presented.

Anaemia in Childhood

RUTH WEGELIUS and MARJATTA KUNNAS

Children's Clinic, Helsinki, Finland

306 children with anaemia were admitted to the hospital during 1 year. The number of children aged 0-1 year exceeded the number of anaemic children aged 2-15 years. About 65 per cent of the anaemic children under 2 years suffered simultaneously from acute respiratory infections.

Anaemia Hypoplastica Congenita (Anaemia Typus Josephs-Diamond-Blackfan)

Report of a successfully Treated Case with Adrenocorticotropin and Cortisone

by ARNE KÄSS and ALFRED SUNDAL

Children's Clinic, Univ. Clinic, Bergen, Norway

A case of anaemia of the Josephs-Diamond-Blackfan type in a 6 year old girl is described. The clinical features were typical, with a marked reticulocytopenia as the most striking haematological finding. She has been dependent on regular blood transfusions with short intervals, most frequently of 4-6 weeks, until the therapy mentioned here was started. After two courses with ACTH treatment there was a marked increase in the reticulocyte count which occurred both times on the 9th day after starting the treatment. It lasted several weeks, accompanied by a spontaneous remission of the blood values. Thus the intervals between the transfusions

have been prolonged for 15 weeks. A third course with ACTH gave the same response and the treatment was continued with Depot-ACTH (long-acting ACTH) twice a week for about 8 months. The next blood transfusion was necessary after $9\frac{1}{2}$ months.

As the patient had been given no treatment for about $2\frac{1}{2}$ months, she had a marked anaemia. In March 1953 peroral cortisone therapy was then started and was followed by a spontaneous rise in blood values up to the normal. The therapy has later been given permanently in variable doses; the minimal dose needed seems to be 5 mg pro die.

18 months have elapsed since the last blood transfusion. The patient is in excellent condition.

The blood values, doses of the drugs, etc. were shown in figures.

Three Cases of Agammaglobulinaemia

by NILS KULNEFF

Central Hospital, Halmstad, Sweden

Infant Mortality

The Infant and Early Mortality in Gothenburg

by YNGVE ÅKERRÉN

Children's Hospital, Gothenburg, Sweden

Continued report (cf. Lecture at the Congress in Helsingfors and Exhibition at the Congress in Stockholm) of the infant and early mortality during the years 1951–53 and a comparison with earlier figures.

Year	Living births No.	Deaths during first year		Deaths during first week		Still-births	
		No.	%	No.	%	No.	%
1941–45	27,154	750	2.76	445	1.64	569	2.05
1946–50	30,947	608	1.96	412	1.33	521	1.66
1951	5,559	107 ¹	1.92	77 ¹	1.39	79	1.40
1952	5,464	103 ¹	1.89	76 ¹	1.39	114	2.04
1953	5,615	63 ¹	1.12	45 ¹	0.80	93	1.66
1951–53	16,638	273 ¹	1.64	198 ¹	1.19	286	1.69

¹ The figures for these years are preliminary.

Infant Mortality in Finland

by HILKKA TÄHKÄ and NIilo HALLMAN

Children's Clinic, Helsinki, Finland

The changes in infant mortality in Finland are shown, pointing out the increased mortality during and shortly after the war and the rapid decrease in the death-rate in the last few years. The infant mortality is at present nearly 3 per cent (in the year 1940, 8.7 per cent). This decrease has been caused mainly by the reduction of all infectious diseases. Infantile diarrhea which has been one of the most important causes of death until recent years, is now practically wiped out. The mortality during the first week of life has not kept pace with the falling infant mortality.

Pneumonia and Hyaline Membranes in Newborn Infants: An Autopsy Material

by K. H. TORP and KR. HARNÆS

*Pediatric Department and the Institute of Pathological Anatomy, University of Oslo,
Oslo, Norway*

The authors have examined 169 stillborn infants and 253 infants who died in the neonatal period. The results are published in the Archives of Disease in Childhood.

Child Psychiatry

One of Identical Twins Presenting Manifest Reading Difficulties

by KARL-HENRIK KARLÉN

*Child Psychiatric Department, Kronprinsessan Lovisa's Children's Hospital,
Stockholm, Sweden*

Tests for Children with Special Difficulties in Reading and Writing

by SVEN AHNSJÖ

School Hygiene Department of the Royal Board of Education, Stockholm, Sweden

The exhibition of tests for reading and writing is a result of an investigation that has been conducted to try to find a simple reading and writing

test as much as possible adapted to its purpose for children with special reading and writing difficulties. It should also be a compensation for all non-standardized tests, which have been used during the 1940's in Sweden and it should also be a compensation for other more incomplete series of tests.

Earlier tests have been given a trial in special (reading) and normal classes in Stockholm during the school years 1948-49 and 1949-50 on 350 children for individual tests and maximum 615 children for group tests in the reading classes 2-5, and on 205 and 322 children, respectively, in the corresponding normal classes 2-5. On the basis of these tests, which have not shown a considerable difference between the two classes, we have been able to form an opinion about their value for estimating the reading and writing difficulties, above all the degree and also in some way the kind of difficulties.

For the tests children have been selected in reading and normal classes from different parts of Stockholm. The results concern the years 1948/50 in the elementary schools of Stockholm. In the other parts of the country such a test cannot be carried out because the system with reading classes has not been developed in the same way there. At this time we thought that in Stockholm we had reached from a pedagogical point of view, a suitable arrangement regarding the clientele in the reading classes and that the admitted frequency of children in these classes would not grow too much in the future. An analysis of these circumstances has now shown that the number of children in reading classes 2-5 during the years 1948-49 to 1952-53 has indeed increased from 482 to 867 but also that this addition on the whole is due to the increase in the number of children and not to a change in the proportion between the number of children in the special and normal classes during these years.

In addition to the above-mentioned tests contemporaneous trial has been made of a test consisting of "mutilated words" and another one with "mutilated pictures", taken from L. L. Thurstone's Gestaltpsychological test series.

This investigation has shown that several of the tests used can be discarded owing to their low differentiating capacity between the children in reading and normal classes.

The tests for reading and writing comprise, class to class, five to six tests for the classes 2-5. The result of the different tests has been given with solution frequencies and averages for reading and normal classes.

Some of the results of the tests with Thurstone's word and picture test complete the series.

The word test with "mutilated words" has proved to be very useful and it is suggested as a suitable basic group-test for teachers when it is a question of selection for ordinary medical psychological examinations. As a support test the picture test with mutilated pictures can be used. The results in the reading classes were approximately the same as in normal classes. The picture test thus shows that the children in reading classes are not handicapped when it is a question of "Gestaltformation" on the visual picture area. This result corresponds well to what we usually find with children with special reading and writing difficulties at intelligence tests according to Terman Merrill where the discrepancy between visual and auditory learning and memory functions can usually be seen very clearly, for example when Terman Merill's profile schedule is used. The maximal results produced in the area of observation are here often higher than the maximal results produced in the acoustic sphere.

The advantages of the exhibited reading and writing test compared with other similar tests lie, among other things, in the comparison between the tested clients' result and the average result in both normal and special classes, for which reason the degree of the tested difficulties can be easier judged.

This like other similar tests is of course meant to come after it is made clear in the usual way that reading and writing difficulties are not secondary to e.g. general mental retardation, visual or hearing defects or similar ailments.

Skeleton

Some Results of Operative Treatment for Craniosynostosis

by L. LAITINEN and M. SULAMAA

Children's Clinic, Helsinki, Finland

When a cranial suture obliterates prematurely, the growth of the large bones of the skull ceases perpendicular to the fused suture and skull deformities occur. When the sagittal suture fuses the skull remains narrow and antero-posterior expansion occurs as a compensatory development, and the typical dolichocephalic or scaphocephalic deformity appears. When the coronal sutures fuse prematurely, the antero-posterior growth from the obliterated sutures ceases. There is a compensatory lateral and vertical expansion of the skull so that brachycephalic deformity or tower skull appears.

The most usual of these synostosis types is the one affecting the sagittal suture. Depending upon the obliteration of one or more sutures together, different types of skull deformities appear.

There are often with this disease other anomalies also, of which syndactylies, very often symmetrical, are the most common.

Sometimes the compensatory growth of the skull is not enough for the brain growth and there will arise—because of the increased intracranial pressure—different symptoms, headache, sometimes convulsions and later visual disturbances, papilledema and optic atrophy, which may lead to total amaurosis. There are often exophthalmos and strabismus which are due to orbital deformities.

The increased intracranial pressure which can be found easily by lumbar puncture may be a factor causing the communicating hydrocephalus, which is common among these patients.

The intelligence of the patients is usually normal. In severe cases there can be mental retardation.

The treatment is operative. Because the weight of the brain has doubled during the 7 first months of life, and has become almost full grown during the three years of life, the operation should be performed as early as the first few months of life.

The general plan of treatment is to perform a linear craniectomy in the region of the fused suture. The margins of this opening are covered with polyethylene film to prevent or retard the rapid regeneration of the bone. The operation is performed under local anaesthesia and it is rather easy to perform.

There has been no operative mortality among the about 150 operations performed in the U.S.A. and in Finland.

The results of the operative treatment have been excellent, when the patient has been treated during the first year of life. The cosmetic results have also been good in patients treated early in life.

At the University Children's Clinic in Helsinki 23 craniosynostosis patients have been treated during 1949–1954 with linear craniectomy ad m. Ingraham. From these 8 cases representing different deformities of the skull have been chosen for the Exposition of the Northern Paediatric Congress in Oslo 1954. The photos and X-ray pictures show the results of the operation. There is also one which has not been operated on.

Chondrodstrophia Calcificans Congenita Punctata ("Stippled Epiphyses")

by ARNE KÅSS

Children's Hospital, University Clinic, Bergen, Norway

This condition was first described by CONRADI (1914). Later about 40 cases have been reported.

There is a mild type of the condition in which the discrete centres of calcification in cartilaginous epiphyses are the only symptom and disappear during the first years of life without leaving any skeletal abnormalities.

The severe type of the condition forms a syndrome consisting of achondroplasia and "stippled epiphyses" together with cataracts and mental deficiency. In these patients pronounced limitation of movement in the joints may be found—giving a clinical picture similar to arthrogryposis multiplex.

At the exhibition three cases were reported.

The first case was a mild type with the stippling of the epiphyses as the only symptom.

The second and third cases were sibs—the only children of young, healthy parents without consanguinity. The mother was well during her pregnancies and she gave birth to her infants with a 17 months interval.

At admission to the hospital, 7 and 6 weeks old, both of the babies showed a completely similar appearance: short, achondroplastic limbs with flexion deformities and cataracts. The radiographs showed stippling of the epiphyses in numerous bones. The first baby was observed in the hospital for about six weeks and died at home 6 months old. The second infant, who also had symptoms of vitium cordis congenitum, was observed until death in hospital at the age of $3\frac{1}{2}$ months. Both of them showed during the observation time a distinct mental retardation.

Serum chemistry gave normal levels of serum calcium, phosphorus and alkaline phosphatase.

Courses of treatment with ACTH and cortisone were not followed by any change in the clinical nor the radiographic pictures.

At the exhibition the case histories were reported and photographs and X-ray pictures of the patients were shown. Pictures of the histological post-mortem findings of the third patient were shown, demonstrating the abnormal picture of the cartilage and the irregularity of the ossification line.

Infantile Cortical Hyperostosis. Development of a Case in Utero

by SIGURD EEK

Radiological Department, Children's Hospital, Rikshospitalet, Oslo

Typical Röntgenograms of a case of infantile cortical hyperostosis of intra-uterine origin are demonstrated, showing considerable periosteal thickening of several bones, most marked in the long canalised bones. These also show to some extent a considerable increase in longitudinal growth—a phenomenon which does not seem to have been described earlier, and which challenges the theory, in vogue at the present time, assuming that this disease depends on tissue anoxia.

Miscellaneous

Accidents to Children in Sweden

by N. BEJEROT and R. BERFENSTAM

Pediatric Clinic, University Hospital, Uppsala, Sweden

Accidents to children are among the most urgent problems of preventive child care. In Sweden death by violence accounts for more deaths than any disease. At certain ages as many children die of accidents as of all the diseases put together.

Pre-school children are hardest hit; especially between two and four years of age children are exposed to great dangers. The material dealing with death by accidents shows that boys clearly predominate. This appears already during the first year of life but becomes more and more pronounced as age increases: in the 10–15 years age group six times as many boys as girls die of accidents.

Drowning accounts for $\frac{1}{3}$ of all deaths, traffic accidents for $\frac{1}{4}$. Among accidents in the home various types of suffocation claim about 30 victims a year, burns the same number and poisoning about ten.

For many years organisations and individuals in Sweden have fought for the prevention of accidents, mainly traffic accidents and drowning. But accidents in the home and other types of accidents occurring in the pre-school stage demand an especially intensive campaign for prevention; in these cases propaganda must go via the home.

A motion in the Swedish Parliament supported increased aid to research and propaganda against accidents in childhood.

Studies of the Respiration and Circulation during the Neonatal Period

by G. BERGLUND, P. KARLBERG and J. LIND

Pediatric Clinic, Karolinska Sjukhuset, Stockholm, Sweden

1) A survey of the normal ventilation (ventilation of the lungs + the gas exchange between the alveolar air and the pulmonary capillary blood) is given. The different static lung volumes with their subdivisions and the different dynamic ventilatory divisions are defined. A schematic diagram shows the respiratory mechanism in a single normal breath. The respiratory function tests, at this time in newborns, are given. The definitions and symbols of respiratory physiology, proposed by the American Standardization Committee (J. R. PAPPENHEIMER *et al.*, *Federation Proc.*, 9: 602, 1950) are introduced.

2) Studies of ventilation and gas exchange during the newborn period are presented (performed at the Boston Lying-in Hospital, Boston, together with C. D. COOK, D. O'BRIEN, R. B. CHERRY and C. A. SMITH). Figures for minute volume, respiratory rate, tidal volume, alveolar ventilation, functional dead space and the energy required for the work of respiration are given for normal newborns and babies in "respiratory distress". (Since the exhibition, this part of the work has been published in *Acta Paediat.*, Suppl. 100: 397, 1954.)

3) Determination of the functional residual capacity in newborns. A method is described and preliminary results given, showing that the functional residual capacity during the newborn period is about one-third of that of an adult, when compared to individual body size. Newborns in "respiratory distress" are found to have a much smaller capacity.

4) Hypothermic treatment in cases of "respiratory distress" is outlined. Two cases with severe pulmonary atelectasis treated in this way are reported. In one of these cases an angiographic study was performed. When the clinical symptoms were most pronounced, a shunt from the right to the left auricle was seen. One month later angiography showed normal circulation.

5) Circulatory studies during the newborn period (together with C. WEGE-LIUS). Schematic diagrams of the fetal circulation and of the different steps during the transformation of the fetal circulation into an adult type circulation are given. Angiographic studies showing the closure of ductus venosus, ductus arteriosus, foramen ovale and the haemodynamics during the newborn period are presented. The transformation of fetal to adult cir-

culation passes through an intermediate state, the neonatal circulatory type, characterized primarily by the functional closures of the fetal circulatory channels, the patency of which can be renewed under adverse conditions. This is shown by angiographic studies in pathologic cases. The change-over of the circulation is intimately associated with the establishment of pulmonary respiration.

Working Capacity in Relation to Age, Sex and Body Weight

by ELIAS BENGSSON

Infectious Diseases Hospital, Stockholm, Sweden

The heart rate increases linearly with the intensity of exercise up to a rate of about 160 beats per minute.

The linear relationship shows a varying deviation in different age groups; it deviates earlier in pre-school children, and somewhat later in older children and adult males. The higher the working capacity, the further the linear relationship reaches.

The maximum working capacity seems to be reached at an average of about 200 beats per minute in untrained individuals between the ages of five and forty. The relationship of heart rate and exercise at rates of up to 160–170 beats per minute indicates the velocity with which the circulatory adaptation approaches, via increasing heart rate, its maximum for adequate circulation.

The exercise performed at any given heart rate can be used as a measure of the velocity with which the heart rate increases with increasing amounts of exercise.

This exercise can be shown in relation to age, body weight, sex, etc.

The working capacity increases linearly with mounting age from the age of five throughout childhood up to the age of twenty. Between the ages of 21 and 40 it is fairly constant, though the individual variations are greater than in children.

The body weight shows major variations in different age groups, and the individual variations will be smaller if the series is grouped according to body weight instead of age, at all events in childhood.

The correlation between body weight and exercise intensity is greater in children than in adults.

In children the correlation between body weight and exercise intensity is $r = 0.85-0.90$ even at such a relatively low heart rate as 130, but in adults this is not the case until a heart rate of 160–170 beats per minute has been

reached. The higher the exercise intensity and the heart rate under steady conditions, the smaller will be the individual variations.

In calculating the working capacity we should take into account notably the age and body weight, but also certain other factors such as degree of training, constitution, balance in the vegetative nervous system, and psychic state.

The sex factor influences the working capacity only in persons over the age of fourteen.

The respiration rate, like the heart rate, shows a linear increase with mounting exercise intensity. Here, however, the linear relationship is less pronounced, at all events in children.

Deviation of this linear relationship varies with age, being earliest in adults and in the oldest children (at about 32 respirations per minute), then later as the age decreases; and in the youngest children—the five or six year olds—the relationship still appears to be linear at 50 respirations per minute. The frequency of respiration is also affected by other factors, however, especially in children. Indeed, the effect here is so marked that calculation of the working capacity by means of this relationship is inadequate, though it may well implement other examinations, for instance in the differential diagnosis of conditions affecting the alveolar diffusion and the pulmonary circulation.

The respiratory minute volume increases linearly with exercise intensity, and the same applies to the oxygen consumption and the amount of carbon dioxide expired. This increase in the oxygen consumption is not dependent on age or body weight, and appears to have the same relationship to the exercise intensity as that earlier described in adults. The net mechanical effect seems to be equal in children and adults.

Since the minute volume of the heart increases linearly with the amount of exercise, and the stroke volume is proportional to the amount of exercise at any given heart rate, it is the maximal stroke volume that is studied under steady conditions in determinations of the heart rate during exercise tests. This stroke volume is dependent, among other things, on the state of the valves and on the contractility of the myocardium. Hence the functional capacity of the heart in myocardial insufficiency and valvular disease can be examined by taking the pulse during bicycle ergometer tests, provided these are carried out with graduated amounts of exercise, over an adequate length of time, and under steady conditions.

Epidermolysis Bullosa Hereditaria Dystrophica

A Genealogical Investigation

by H. ENELL and M. PEHRSON, Boden, and B. HALLGREN, Stockholm

Pediatric Dept., Military Hosp., Boden, Sweden

Epidermolysis bullosa is a rare, hereditary, well-defined disease, which appears in three main forms of varying severity. The milder forms are genetically dominant and the most serious recessive. Concerning the intermediate forms, the so-called dystrophic types, which do, however, cause a significant degree of invalidity, there are divergent points of view as to the mode of inheritance, and genetic analyses seem to confirm that both types of heredity occur.

Taking the case of a patient treated at the Pediatric Department, Garnisonssjukhuset, Boden, the demonstrators have tried to make as complete a genealogical analysis of the relatives as possible. The genealogy of 747 persons was studied and 6 secondary cases of epidermolysis bullosa hereditaria dystrophica were discovered. Altogether the material consists of 7 cases belonging to 6 families. In 5 of these families the parents were related and it was in these cases possible to chart the probable heterozygote lines. Since the group has lived in an isolated region, it has in certain cases been possible to trace back the ancestry for eight generations. Intermarriage within the family has occurred frequently. Of the affected persons 3 were boys and 4 girls, while the healthy siblings included 12 boys and 7 girls. The material is insufficient for Mendelian analysis. In this particular group heredity undoubtedly points to a monohybrid recessive inheritance.

The demonstration material consists of a pedigree chart as well as short case histories, clinical data and some photographs of the affected children.

Vitamin D Intoxication

by BJARNE ANDERSEN

*Pediatric Department, Ullevål Hospital, Oslo, Norway
(Publ. in "Tidsskrift for Den Norske Lægeforening" 12: 1954, 419)*

Four cases of intoxication with Vitamin D (Calciferol) are reported. The children were 16 months to 5 years old. No. 1 and No. 2 received large doses within a short time (10 million U. in 6 weeks and 3 mill. U. in 2 weeks). Both recovered rapidly when Calciferol was discontinued. No. 3

and No. 4 got smaller daily doses, but treatment was continued over a very long period (25 mill. U. in 1 year and $12\frac{1}{2}$ mill. U. in $\frac{1}{2}$ year). After discontinuing the vitamin for 17 weeks in cases 3 and 4, the children still had their symptoms nearly unchanged.

All the patients had gastric and renal impairment signs, hypercalcaemia and increased blood-urea.

Three had band-keratitis (Nos. 2, 3 and 4). Two (Nos. 3 and 4) had changes in the roentgenograms of the long bones.

Radiological Findings in Cases of Infantile Hypertrophic Stenosis of the Pylorus

by SIGURD EEK

Radiological Department, Children's Hospital, Rikshospitalet, Oslo, Norway

In the overwhelming majority of cases infantile hypertrophic stenosis of the pylorus involves only the canalis part of the stomach. The duodenal bulb, with its duodenal pyloric part, is not involved, and patient No. 1 is a fair sample. This condition ought therefore to be called infantile hypertrophic canalic stenosis.

The whole of the canalis part of the stomach is hypertrophied, and the stenosis is usually of a stereotyped, thread-like character undergoing little variation. It is quite exceptional to find peristaltic waves in the beginning of the canalis as in patient No. 2. In a long series of cases more or less prolapse of the gastric mucosa had reached the duodenal bulb so as to give it the shape of a parachute as in patients Nos. 3 and 4. This prolapse disappears on recession of the stenosis. It is not rare to find ulcers of the mucosa in the juxta-pyloric part of the canalis as the result, in all probability, of trophic disturbances. Patient No. 4 is an example of this condition. These ulcers disappear soon after the stenosis has been corrected.

Technique.—Through a naso-gastric tube some 15 ml of a barium contrast are introduced into an empty stomach. Thereupon the patient is examined as soon as possible in an upright position, hanging in a bag, before the contrast fills the pars ascendens and covers the canalis area. In cases of retention the patient is also examined after 3 and 24 hours.

Placental Dysfunction in Postmaturity

by PER SELANDER

Flensburg's Children's Clinic, Malmö, Sweden

Of 1,330 children examined at the Women's Clinic in Malmö 12.0 per cent exhibited dry, macerated, wrinkled skin, especially on the palms of the hands and the soles of the feet, brown pigmentation of the nails and the umbilical cord, intense erythema of the external genitals and desiccation ("Ballantyne-Runge's syndrome"). Of the children who were born more than 4 days after the calculated date 20.3 per cent had the syndrome, whereas of those who were born less than 4 days before the calculated date 3.2 per cent displayed the syndrome. Of the 160 children with the syndrome 58.8 per cent were postmature by more than 4 days. Of those with a pronounced syndrome 73.0 per cent were postmature more than 4 days.

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IMPLICATIONS OF AGENESIS OF THE SPLEEN ON THE PATHOGENESIS OF CONO-TRUNCUS ANOMALIES IN CHILDHOOD

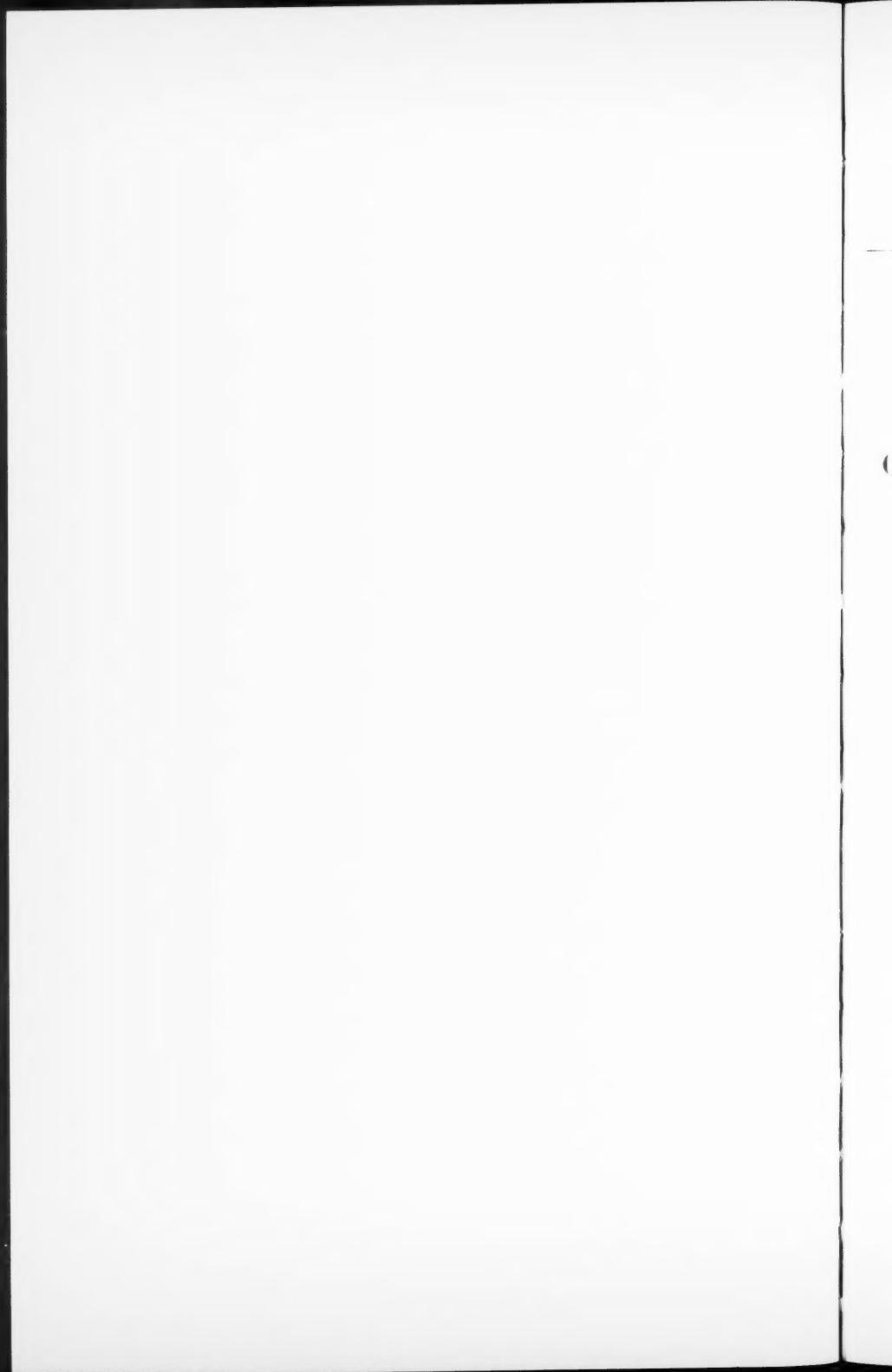
An Analysis of the Heart Malformations in the Splenic
Agenesis Syndrome, with Fourteen New Cases

By

BTÖRN I. IVEMARK

Almqvist & Wiksell's Boktryckeri AB UPPSALA

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AND THE PEDIATRIC CLINIC, KAROLINSKA SJUKHUSET, STOCKHOLM
(CHIEF: PROFESSOR ARVID WALLGREN).

IMPLICATIONS OF AGENESIS OF THE SPLEEN ON THE PATHOGENESIS OF CONO-TRUNCUS ANOMALIES IN CHILDHOOD

An Analysis of the Heart Malformations in the Splenic
Agenesis Syndrome, with Fourteen New Cases

by

BIÖRN I. IVEMARK



Printed in Sweden
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Stockholm 1955

To my Father and Mother

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Preface

This study was begun and the major part of it was carried out in 1953 at the Department of Pathology, Children's Hospital, Boston. The chief of that department, Professor Sidney Farber, and his staff showed a continuous and stimulating interest in my work. Professor Farber gave me generous permission to include in this study all the cases of absence of the spleen and certain other cases of splenic malformations from that department. Professor Farber and Doctor Betty B. Geren have given helpful and detailed criticism of the manuscript.

The final stages of my work, the taking of the photomicrographs and the compilation of all data have been completed at the Department of Patho-Anatomy, Karolinska Sjukhuset, Stockholm. The chief of that department, Professor Åke Wilton, has put all the facilities of his institution at my disposal and has besides given valuable criticism of my manuscript. Professor Wilton, and Docent Bengt O. Engfeldt and Docent Kaj H. R. Lindberg of his staff have shown great interest in my study and have never failed to encourage its completion.

Professor Gösta Häggqvist, chief of the Department of Histology, Karolinska Institutet has generously offered for my study all the embryos described. Professor Häggqvist has also checked the slides for presence of splenic primordia and has given many valuable suggestions concerning their description and relative age. Docent Lars Gyllensten of his staff has critically reviewed the sections on embryology.

Professor Nils Ringertz, chief of the Department of General Pathology, Karolinska Institutet, and my former chief, has closely followed this study from its initiation to its completion. By personal guidance and constant stimulation he has helped me through the final stages of the study. In addition, Professor Ringertz has given me permission to include Case 1.

The chiefs of the two Pediatric Clinics at Karolinska Institutet, Professors Curt Gyllenswärd and Arvid Wallgren, have shown interest in my work and great understanding of the time-consuming final stages of this study.

Docent Sven Roland Kjellberg and Docent Lars A. Werkö have made valuable suggestions and constructively criticized the manuscript. Docent Gunnar Ekström has generously discussed the clinical and surgical view-

points. Doctors Håkan Arvidsson, Erik Berglund, Docent Rolf Zetterström and Doctor Thor Alm have all given valuable suggestions during long discussions.

The statistical calculations have been made by Thøger Busk, Ph.D., the Department of Statistics, University of Copenhagen.

Doctor Daniel Stowens, Armed Forces Institute of Pathology, Washington, D.C., has given me permission to include Case 7.

The gross photographs were taken by Mr. Ferdinand R. Harding and his assistants at the Children's Hospital, Boston.

Mrs. Astrid Binett has given efficient secretarial aid.

Miss Ruth B. Cherry, M.A., has gone over the manuscript from the language point of view.

To all the above I extend my warmest thanks.

My wife, Barbro, has given technical assistance in serially sectioning many embryos in the search for early splenic primordia, and she has shown inexhaustible patience throughout the work. To her I give my heartfelt thanks.

I am greatly indebted to the Rockefeller Foundation for the fellowship which made possible the year of study at the Children's Hospital, Boston.

Finally, I express my gratitude to the printers at Ivar Häggströms Boktryckeri AB for their helpful cooperation.

Stockholm, October 1955.

Björn I. Ivemark

Introduction

Until recently, little attention has been paid to malformations of the atrio-ventricular region in cases with anomalies of the cono-truncus. Malformations of the latter have usually been studied separately and by comparisons among cases displaying various anomalies of the cono-truncus. With the exception of tricuspid and mitral atresia, malformations of the atrio-ventricular valves have usually not been studied in association with malformations of the cono-truncus.

Recently, *Shaner* (1949) pointed out the frequent occurrence of malformations of the atrio-ventricular canal cushions in cases of congenital malformations of the heart in pig embryos. This author carried out microdissection on 20,000 embryo pigs (1951). By this approach *Shaner* caught the anomalous heart in an earlier stage of malformation than had been achieved before. *Shaner* found 48 embryos with malformed hearts. A large percentage of these had anomalies of the cono-truncus associated with malformed atrio-ventricular canal cushions. *Shaner* considered the former to be caused by the latter.

That this also might be the case in human hearts with anomalies of the cono-truncus has been emphasized by *Doerr* (1952, a and b). That author stresses the frequent association of atrio-ventricular anomalies and congenital pulmonary or aortic stenosis.

This paper deals with the problem of whether there is any relationship between anomalies of the two mentioned regions in the heart. Cases of cardiac malformations associated with agenesis of the spleen will be analyzed. By this method of selection, not applied to cardiac malformations before, far-reaching conclusions can be drawn concerning the pathogenesis of certain types of malformations of the cono-truncus region. This is due to the fact that during embryogenesis the spleen is being formed while the heart is still in a stage of critical modeling. By selecting cases of cardiac malformations associated with absence of the spleen, it is postulated that cases are collected in which the basic lesion of the heart during organogenesis occurred while the spleen should have been in its early formative stage of development. Thus, the uniformity of the material is based upon selecting the period when organogenesis of the heart went astray, rather than on similarities in morphology of the malformed hearts.

Congenital heart disease associated with absence of the spleen is usually combined with varying degrees of situs inversus (*Putschar*, 1934). During the 19th century, situs inversus associated with malformations of the heart was studied extensively by pathologists (for references, see *de F. Bauw*, 1944). Among the 20th century cardiologists, "levocardia with subdiaphragmatic lateral heterotaxy" likewise attracts considerable attention (*Forgacs*, 1947; *Robinson & Garsinkle*, 1950; *Thomson*, 1950; *Young & Griswold*, 1951; *Campbell & Forgacs*, 1953).

Malformations of the heart and great vessels in situs inversus are complex, and the anatomic variation from case to case is considerable. Cases lacking a spleen within this group, however, may seem fairly uniform in their anatomic pattern; hence, such cases have recently been considered as constituting a "syndrome" (*Polhemus & Schafer*, 1952; *Gasser & Willi*, 1952; *Boggs & Reed*, 1953; *Baumann*, 1954; *Ivemark*, 1955; *Willi & Gasser*, 1955).

This paper contains four main parts. In the first, the embryology of the cono-truncus and the atrio-ventricular canal at the time of early splenic organogenesis will be reviewed. The author's own contribution in this part includes brief descriptions of the splenic primordia of six human embryos. These embryos have been dated in correspondence with the age groups of *Streeter*. The synchronous developmental levels of other pertinent organs are mentioned. The syndromic nature of embryology is applied. The role of hemodynamic forces in the septation of the cono-truncus is emphasized.

In the second part, the pathology of the splenic agenesis syndrome is described, and 14 new cases with autopsy are reported. It is maintained that the cases constitute examples of a "teratologic syndrome".

The third part deals briefly with cases of congenital heart disease associated with hypoplasia of the spleen and similar cases with multiple spleens.

In the fourth part, the pathogenesis of malformations of the cono-truncus in relation to those of the atrio-ventricular region is discussed. The facts presented are in favor of the concept that atrio-ventricular anomalies may be primary to certain malformations of the cono-truncus.

PART I

Temporal Relations between Splenic Formation, Cono-Truncus Development, and Division of the A-V Canal

For descriptive purposes, embryology can be studied in two different ways. Most commonly, each organ system is traced separately from its early primordia throughout embryonic life. By this method the successive changes in that organ system may be followed closely, and the evolution of a given system is made comprehensible. In the other method, all organs are studied together in age groups in a parallel fashion so as to encompass the interrelations of all organs in embryogenesis. By the latter method, emphasis is placed on the dependence of one organ upon another in morphogenesis. The first-mentioned approach is commonly used for didactic purposes in textbooks of embryology. The second method may reveal interesting interrelations in the morphogenesis of various organs.

The first attempt at systematizing early human embryos into stages of development, or age groups, was made by *Mall* in 1914. Material from the literature and from the Carnegie Embryological Collection in Baltimore was used. Greatest length (G.L.) and external appearance constituted the criteria for grouping. *Mall* found, however, that the material was too scarce to fulfill this plan. Not until 1942 was the project of *Mall* continued by *Streeter* in his paper, "Developmental Horizons in Human Embryos". In the intervening twenty-eight years, the Carnegie Collection had acquired many embryos. In addition, valuable data had accumulated on the timing of rhesus embryos, forming reliable information about the age of primate embryos.

On the assumption that organogenesis is interrelated, *Streeter* based his age grouping on the appearance of certain characters the combination of which constituted a "horizon". The term horizon was chosen by *Streeter* in analogy with archaeology and geology to emphasize "the embryo as a living organism which in its time takes on many guises, always progressing from the smaller and simpler to the larger and more complex" (*Streeter*, 1942, p. 214).

Since very early human embryos were very few in 1942, *Streeter* started with Horizon XI, "13 to 20 somites present", and reserved the designations

I—X for the earlier stages of development, planned so as to encompass the "One-celled egg" (Horizon I) through "Early somites present" (Horizon X).

In 1948, after having covered eight horizons (XI—XVIII), Streeter had confirmed the original idea of embryogenesis' being characterized by a definite and invariable schedule of organ correlation. At any horizon there was a syndrome of features characteristic for that level of development, and the presence of any one of these characters in an embryo indicated the presence of the others.

The definitions of the various horizons consist of scoring points, well defined and easily recognizable on the slides. The age of the embryos was calculated by comparison with macaque embryos of known ovulation age.

Unfortunately, Streeter in his horizons never mentions the appearance of the spleen. This organ does not constitute a scoring point for the characterization of any horizon.

A. The Author's own Investigations on the Early Appearance of the Spleen

As the splenic primordia are not mentioned in *Streeter's* papers, the author has undertaken to study the early appearance of the spleen in relation to the age groups of *Streeter*. Thus, six embryos (Collection of the Department of Histology, Karolinska Institutet) were studied, measuring 9—12 mms. in greatest length (G.L.). All embryos except one had been fixed in formalin; the remaining one, in Carnoy's fluid. They were all well preserved and serially sectioned. They are listed in Table 1. These six embryos showed evidence of splenic primordia in the left aspect of the dorsal mesogastrium.

TABLE 1. Serially sectioned embryos showing splenic primordia

Embryo	G.L.	Sectioning	Section thickness	Fixation	Horizon	Figs.
A	9 mms.	Transversely	10 microns	Carnoy	XV	1—3
Ser. 24	9 mms.	Transversely	10 microns	Formalin	XV	4—6
Ser. 31	9 mms.	Transversely	10 microns	Formalin	XVI	7—8
No. 20	9 mms.	Transversely	10 microns	Formalin	XVI	9—10
Ser. 10	11 mms.	Sagittally	5 microns	Formalin	XVII	11—13
Ser. 32	12 mms.	Transversely	10 microns	Formalin	XVI	14—16



Fig. 1. Embryo A, 9 mms. In the left aspect of the dorsal mesogastrium an area of undifferentiated mesenchymal swelling is seen. This is the area of the future spleen. x38.



Fig. 2. Embryo A, 9 mms. The dorsal mesogastrium in higher magnification. There is no cytologic differentiation in the mesenchyme. Note the similarity in structure between the stomach wall and the future spleen. No angiogenesis is seen. x136.



Fig. 3. Embryo A, 9 mms. The lens vesicle of the eye is closed. x38.



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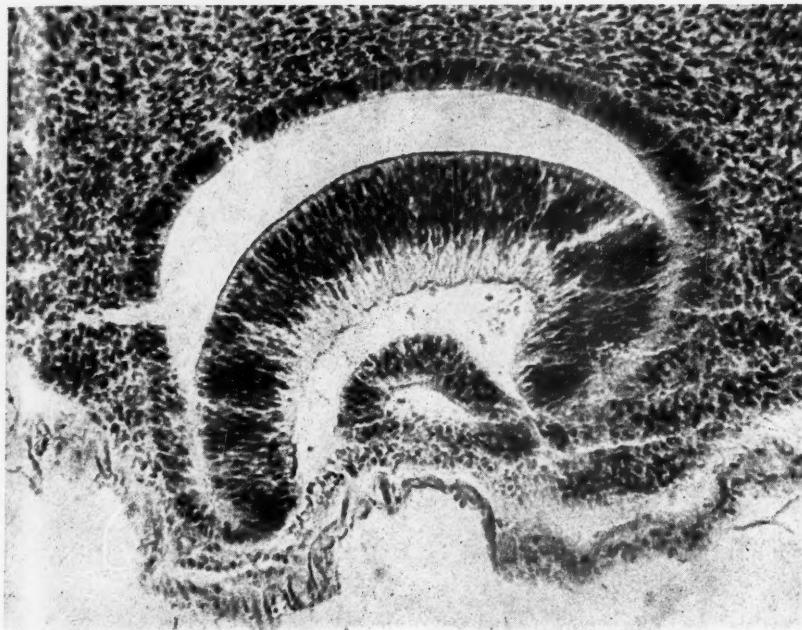


Fig. 5. Embryo Ser. 24, 9 mms. The lens vesicle of the eye is closed. x38.

Embryo A, 9 mms. (Collection of the Department of Histology, Karolinska Institutet), was serially sectioned transversely after fixation in Carnoy's fluid. The sections are 10 microns thick and stained with hematoxylin-eosin. The embryo is in excellent preservation.

The dorsal mesogastrium was thickened and showed an area of bulging to the left (Fig. 1). It was clearly separated from the dorsal wall of the stomach by a recess. The thickened dorsal mesogastrium had the appearance of undifferentiated mesenchyme. Cytologically, this area was indistinguishable from the stomach wall (Fig. 2). There was no evidence of angiogenesis. In view of the thickening, this area was interpreted to be early splenic primordia. Morphologically, this splenic *anlage* was the least differentiated in the present series.

Fig. 4. Embryo Ser. 24, 9 mms. Early splenic primordia in dorsal mesogastrium. Note small areas of early angiogenesis. x136.

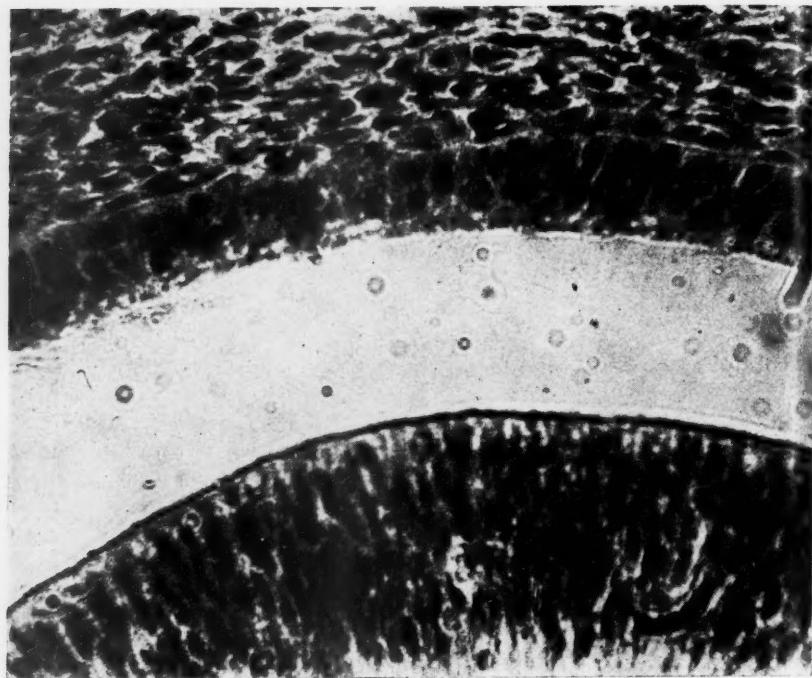


Fig. 6. Embryo Ser. 24, 9 mms. The outer layer of the retina shows no pigment granules. x460.

The following criteria showed this embryo to be a member of Horizon XV of Streeter. The lens vesicle was definitely closed (Fig. 3). There was no pigment in the outer layer of the retina. There was no migration of the inner retinal cell nuclei.

Embryo A (9 mms.) belonged to Horizon XV and showed an area of undifferentiated thickened mesenchyme in the left aspect of the dorsal mesogastrium, interpreted as early splenic primordia.

Embryo Ser. 24, 9 mms. (Collection of the Department of Histology, Karolinska Institutet), was likewise sectioned serially and transversely. It had been fixed in formalin. The sections are 10 microns thick and hematoxylin-eosin stained. The embryo is in excellent preservation.

In the thickened dorsal mesogastrium there was a bulge to the left. This thickened dorsal mesogastrium was well separated from the stomach wall by

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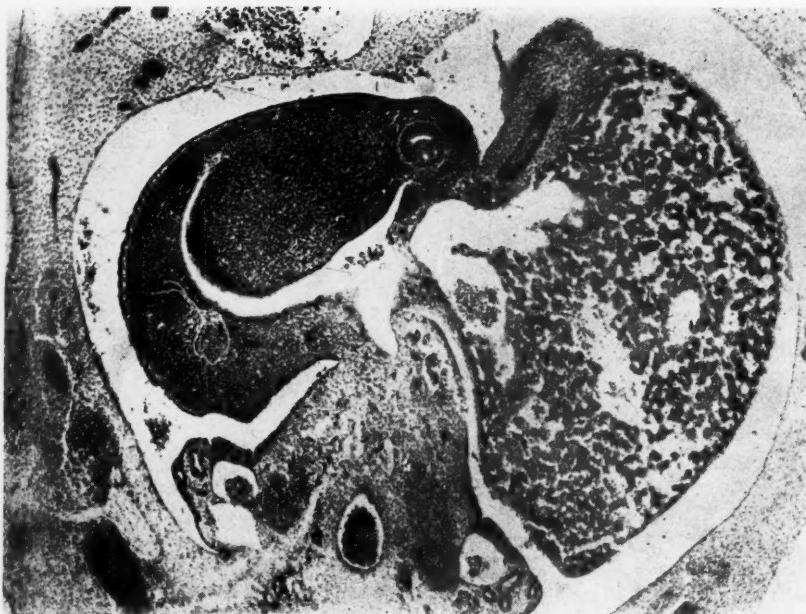


Fig. 7. Embryo Ser. 31, 9 mms. Early splenic primordia are seen in the thickened dorsal mesogastrium. x55.

a recess, similar to that described previously in Embryo A. In the thickened part there were small areas of angiogenesis (Fig. 4). No clear-cut sinusoids were present. The part of the dorsal mesogastrium described was considered to be early splenic primordia.

This embryo was also shown to be a member of Horizon XV. The lens vesicle was closed (Fig. 5). There was no pigment in the outer layer of the retina (Fig. 6). No evidence of migration of the inner retinal cell nuclei was present.

Embryo Ser. 24 (9 mms.) belonged to Horizon XV. It showed evidence of early splenic primordia in the left aspect of the dorsal mesogastrium with small areas of angiogenesis but without sinusoids.

Embryo Ser. 31, 9 mms. (Collection of the Department of Histology, Karolinska Institutet), was serially sectioned transversely after formalin fixation. The sections are 10 microns thick and hematoxylin-eosin stained. The embryo is in excellent preservation.

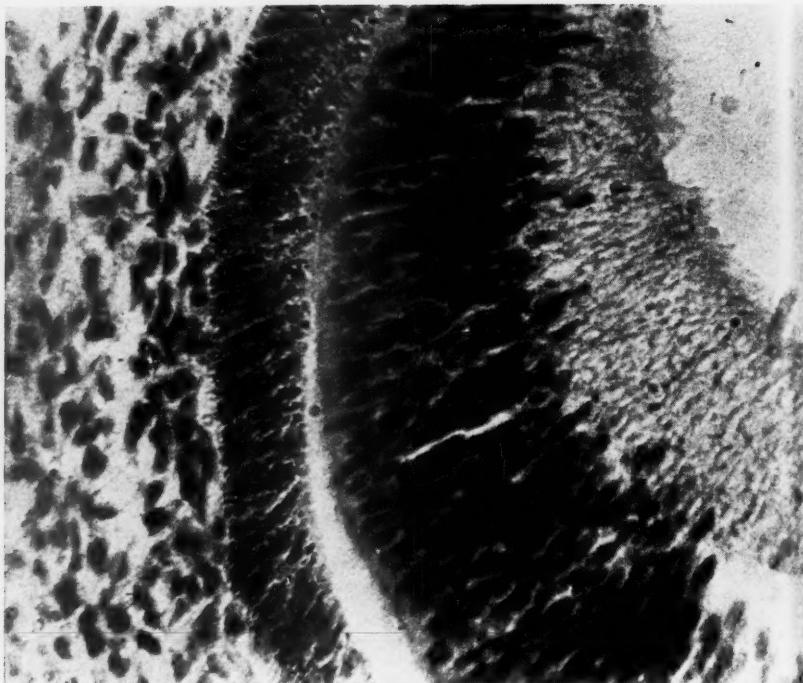


Fig. 8. Embryo Ser. 31, 9 mms. In the outer layer of the retina pigment granules without clustering or peripheral migration are seen. In the inner retinal layer there is no migration of nuclei. x675.

The dorsal mesogastrium was greatly thickened (Fig. 7). There was a bulge to the left. This area of bulging was considered to be early splenic primordia. Angiogenesis was clearly seen and was more prominent in this embryo than in the previously described Embryo Ser. 24. In addition, occasional small sinusoids lined with thin endothelium were encountered.

This embryo belonged to Horizon XVI. The lens vesicle was closed. There were pigment granules in the outer layer of the retina, without clustering or peripheral migration (Fig. 8). There was no migration of the inner retinal cell nuclei. The A-V canal cushions were fused. There was a primitive gut mesentery.

Embryo Ser. 31 (9 mms.) belonged to Horizon XVI. It contained splenic primordia in the left aspect of the dorsal mesogastrium. There were angiogenesis and small endothelium-lined sinusoids.

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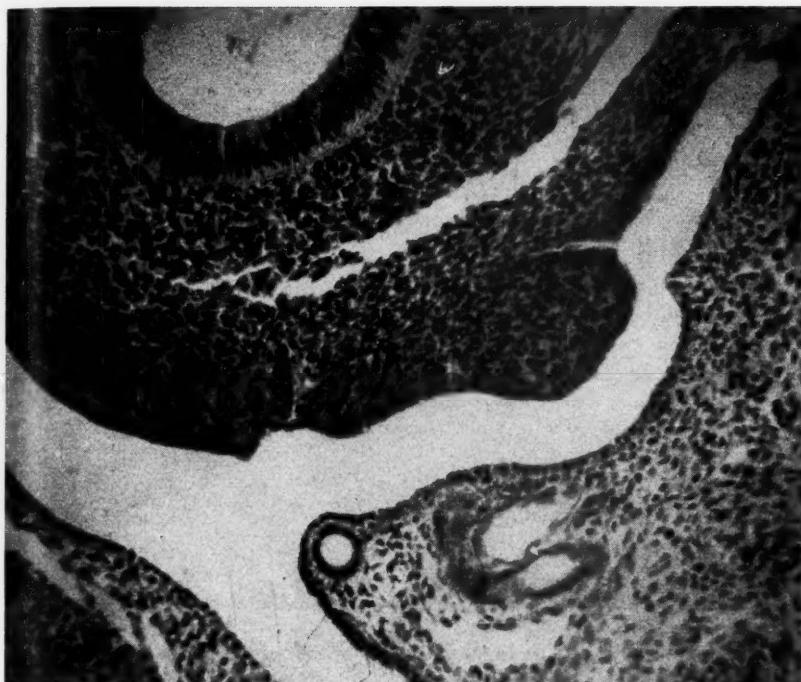


Fig. 9. Embryo No. 20, 9 mms. Splenic primordia in left aspect of dorsal mesogastrium. To the right there is a small incisure on the surface. x136.

Embryo No. 20, 9 mms. (Collection of the Department of Histology, Karolinska Institutet), was serially sectioned transversely after formalin fixation. The sections are 10 microns thick and hematoxylin-eosin stained. The embryo is in excellent preservation.

The left aspect of the dorsal mesogastrium was thickened. The early splenic primordia showed angiogenesis and there were occasional sinusoids present. On the surface there was evidence of early notching. In Fig. 9 an incisure is seen to the right. These splenic primordia appeared more mature than those described previously in this series.

The following characteristics showed the embryo to be a member of Horizon XVI. There were definite pigment granules in the outer layer of the retina (Fig. 10), without clustering or migration peripherally. In the inner retinal layer very occasional nuclei showed migration. The posterior lobe of

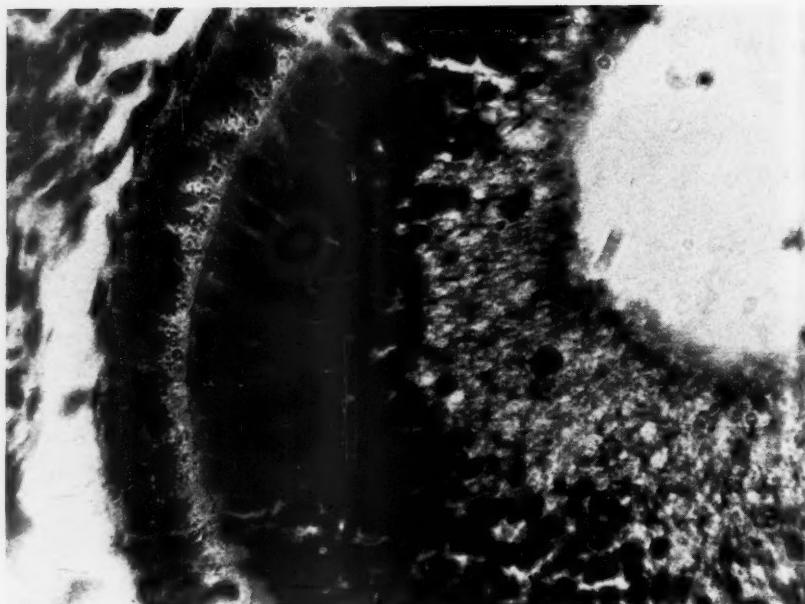


Fig. 10. Embryo No. 20, 9 mms. In the outer layer of the retina pigment granules without clustering or peripheral migration are seen. In the inner layer very occasional nuclei show migration toward the center of the eye. x675.

the pituitary was beginning to evaginate. The A-V canal cushions were fused. There was an epithelial bronchial tree and a primitive gut mesentery.

Embryo No. 20 (9 mms.) belonged to Horizon XVI. Splenic primordia were present in the left aspect of the dorsal mesogastrum, with evidence of notching. There were angiogenesis and small sinusoids.

Embryo Ser. 10, 11 mms. (Collection of the Department of Histology, Karolinska Institutet), was serially sectioned sagittally at 5 microns after fixation in formalin. It is hematoxylin-eosin stained. It shows excellent preservation.

The dorsal mesogastrum contained a bulge to the left (Fig. 11). In this area, considered to be the splenic primordia, there was prominent angiogenesis. Several sinusoids lined with endothelium were present. This early spleen was the most differentiated of the splenic primordia described in this series.

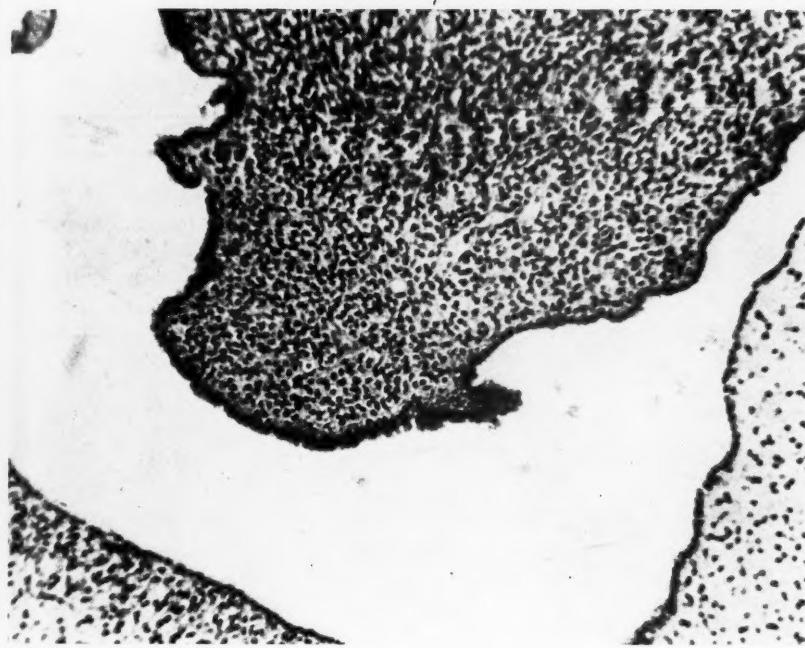


Fig. 11. Embryo Ser. 10, 11 mms. Splenic primordia with prominent angiogenesis and early sinusoids. x136.

The following criteria showed this embryo to be a member of Horizon XVII. There were pigment granules in the outer layer of the retina with clustering and migration peripherally (Figs. 12—13). Migration of some of the inner cell nuclei had occurred in the retina (Fig. 12). The A-V canal cushions were fused. In the bronchial tree there was evidence of branches of secondary order, the initiation of pulmonary lobation. There were well marked calyces in the kidneys.

Embryo Ser. 10 (11 mms.) belonged to Horizon XVII. Splenic primordia, with prominent angiogenesis and several sinusoids, were present. These primordia appeared to be the most mature in the series described.

Embryo Ser. 32, 12 mms. (Collection of the Department of Histology, Karolinska Institutet), was serially sectioned transversely after formalin fixation. The sections are 10 microns thick and hematoxylin-eosin stained. The embryo is in excellent preservation.



Fig. 12. Embryo Ser. 10, 11 mms. In the outer layer of the retina there are pigment granules with clustering and peripheral migration. The inner retinal cell nuclei show migration toward the center of the eye. x675.

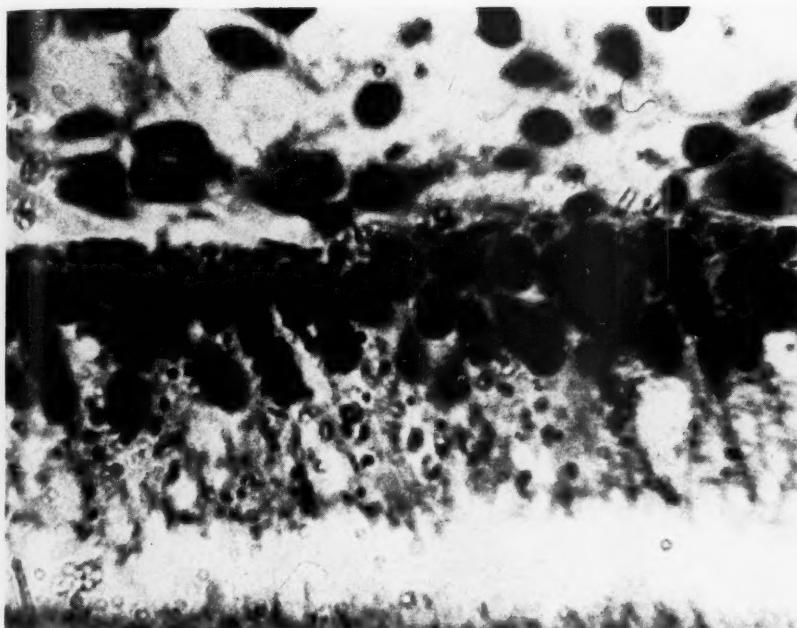


Fig. 13. Embryo Ser. 10, 11 mms. The pigment granules in the outer layer of the retina show clustering and peripheral migration. x1020.

The left aspect of the dorsal mesogastrium was greatly thickened (Fig. 14). The early splenic primordia were the site of angiogenesis (Fig. 15), and there was cellular condensation in this area as compared with the stomach wall. A few sinusoids were encountered

This embryo belonged to Horizon XVI. There were pigment granules in the outer retinal layer, without clustering or migration toward the periphery (Fig. 16). There was no migration of the inner cell nuclei of the retina. The posterior lobe of the pituitary was beginning to evaginate. The A-V canal cushions were fused. In the bronchial tree no clear-cut branches of secondary order were found. There was a primitive gut mesentery.

Embryo Ser. 32 (12 mms.) belonged to Horizon XVI. There were splenic primordia with angiogenesis and a few sinusoids. This embryo was less mature, morphologically, than Embryo Ser. 10, previously described.



Fig. 14. Embryo Ser. 32, 12 mms. The splenic primordia are seen in the left aspect of the dorsal mesogastrium in lower center of picture. x38.

In summary, splenic primordia have been shown to be present in six human embryos belonging to Horizons XV—XVII. The first morphologic evidence of such primordia consists of an area of mesenchymal thickening in the dorsal mesogastrium. This occurs in Horizon XV. Small areas of angiogenesis but no sinusoids may be found in this horizon. In Horizon XVI there is evidence of increasing angiogenesis, and the first sinusoids appear. In Horizon XVI, as seen in one embryo (No. 20), there may be incisures of the surface of the splenic primordia. In Horizon XVII sinusoids are more prominent.

These findings are in accordance with statements in the literature. *Arey* (1954) describes the swelling of the dorsal mesogastrium as occurring in embryos of 8 mms. greatest length. *Broman* (1927) gives the greatest length as 10 mms. *Kollmann* (1907) states that the length is 10.5 mms.; *Hamilton, Boyd & Mossman* (1952), 10 mms.; and *Starck* (1955), 10 mms.

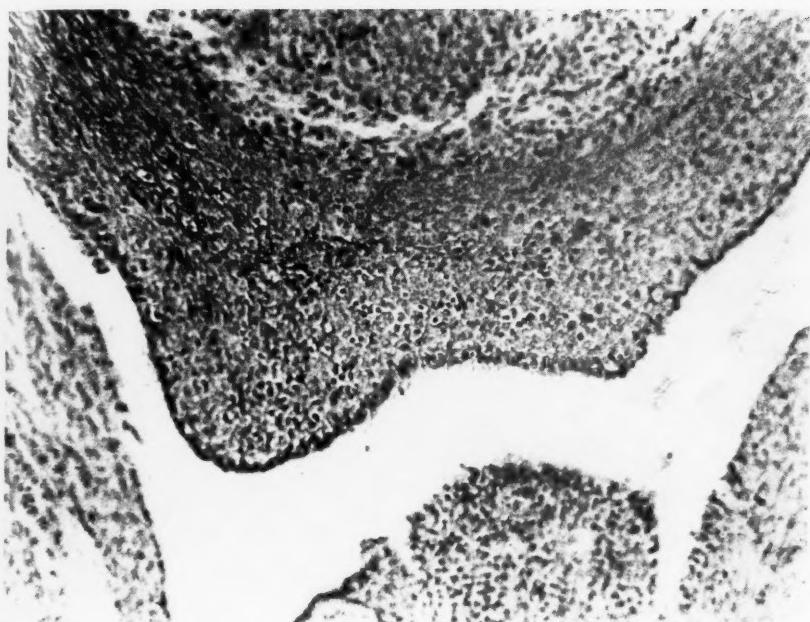


Fig. 15. Embryo Ser. 32, 12 mms. Higher magnification of splenic primordia. Angiogenesis is evident. x136.

The notching of the surface is said by *Broman* (1921) to occur in the latter part of the third embryonal month. However, in one of the human embryos described by the writer, incisures appeared in Horizon XVI. This would correspond to an ovulation age of 32—34 days. *Clatworthy & Anderson* (1944) state that the mesenchyme in the dorsal mesogastrium starts to proliferate and becomes vascularized in the sixth embryonal week, and that blood spaces and notching form in the third embryonal month. The varying figures for the greatest length of the embryo at the time of the appearance of the splenic primordia are evidence for the usefulness of the horizontal concept of *Streeter* as far as the estimation of the developmental level is concerned.

As the earliest discernible stage of spleen formation appears to be a swelling of the dorsal mesogastrium and a condensation of its cells, the morphologic evidence of the presence of the "first" splenic *anlage* by definition is subjective and unreliable. It seems very likely that histochemical

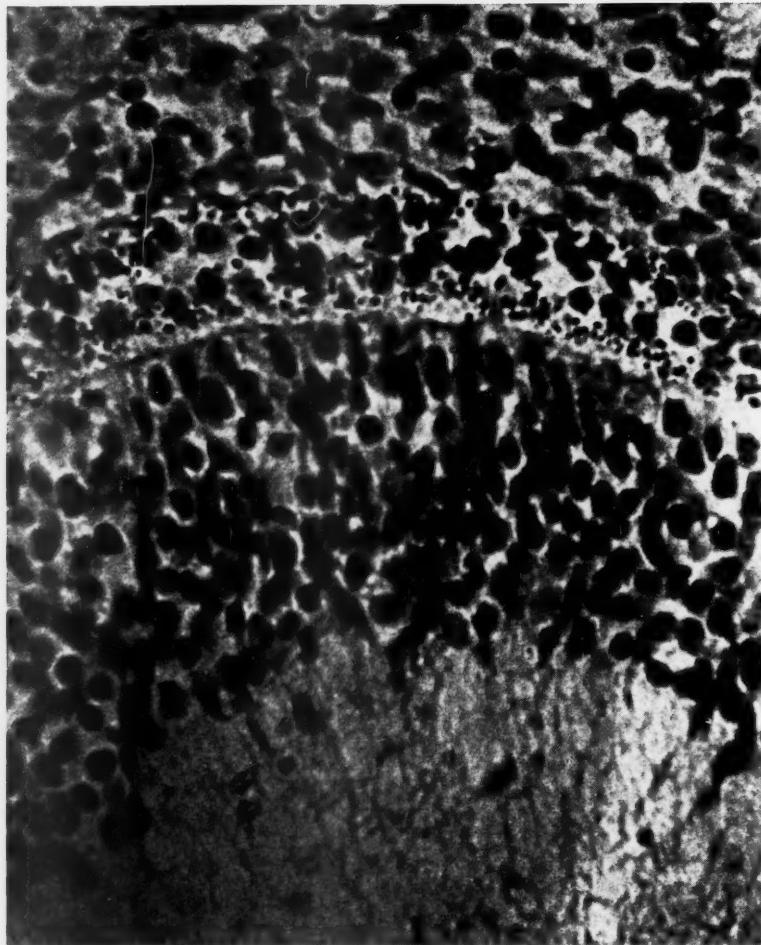


Fig. 16. Embryo Ser. 32, 12 mms. In the outer layer of the retina pigment granules without clustering or migration are seen. In the inner layer there is no evidence of nuclear migration. x675.

methods would enable us to locate the splenic primordia even earlier, if there were a known specific stainable substance in them. Besides, in formalin fixed, paraffin embedded and hematoxylin-eosin stained preparations no histochemical studies are possible. However, as the spleen is known to grow

very rapidly (*Patten*, 1953 a), it seems probable that it is in its early formative stage in Horizons XV—XVI. The exact dating of the earliest appearance of the splenic primordia would need a large material and would call for various techniques for exact localization, for example, analogous with the histochemical studies on germ cells by *McKay et al.* (1953).

As the early formative stage of splenic organogenesis can be assumed to occur around Horizon XVI, this part of embryogenesis will be reviewed briefly. Particular attention will be paid to the cono-truncus and the atrio-ventricular canal, as the interrelation of these structures forms the body of this paper.

B. On the Morphogenesis of the Cono-Truncus and the A-V Region at the Time of Early Splenic Organogenesis

In the following sections *Streeter's* timing of embryos will be adopted. Other systems of dating early embryos have been published by, for example, *Patten* (1953 a). *Streeter's* (1948) criteria for *Horizon XV* were deduced from data on 25 embryos, 18 of which had a greatest length varying from 6.5—8.5 mms. The estimated ovulation age was between 31 and 32 days as calculated from comparisons with macaque embryos of known ovulation age. This method of estimation of age was the same in all horizons to be described.

The criteria for *Horizon XVI* were obtained on 36 embryos, 24 of which had a greatest length of between 8 and 11 mms. The calculated ovulation age was 33 ± 1 days for the group.

Horizon XVII was composed of 25 embryos, 17 of which had a greatest length of 11.0 to 13.6 mms. The calculated ovulation age was 35 ± 1 days.

Horizons XV, XVI, and XVII are thus separated by approximately two days each. During the six days covered by Horizons XV—XVII, the early splenic primordia have been shown to exist. As will be pointed out later, the critical modeling of the cono-truncus and the atrio-ventricular canal occurs at this time in embryogenesis.

On the division of the cono-truncus

According to *Streeter* (1948), the spiraling septum dividing the truncus arteriosus starts to grow from the distal end of the truncus during the XVth Horizon, is well under way but not completed in Horizon XVI, and separates the pulmonary trunk from the aorta in Horizon XVII. The septum is formed by ingrowth of the gelatinous reticulum of *Streeter* (*Kramer* 1942; *Streeter*, 1948; *Patten*, 1953 b), a descriptive term preferred by the writer to the

"embryonal connective tissue" or the "endocardial cushion tissue" used by other authors. The cardiac jelly (*Davis*, 1924 and 1927) is converted to gelatinous reticulum when it shows evidence of cells, *i.e.*, nuclei.

That the truncus septum is spiral in its growth is well established (*e.g.*, *Kramer*, 1942). Whether the spiraling course is genetically determined or whether hemodynamics plays a part in its modeling is, however, still controversial. Self-differentiation of explanted or heterotopically transplanted hearts deprived of their circulation has been demonstrated in numerous publications (for references, see *Copenhaver*, 1955). The explanted hearts have been reported as not being old enough, however, to display differentiation of the cono-truncus, and it is not yet known whether self-differentiation and septation of the cono-truncus can occur in hearts lacking blood circulation. *Stöhr* (1925) and *Bremer* (1928 and 1931) have shown in amphibians and birds that the blood stream has an effect on the differentiation of the cono-truncus in the later stages of development. *Streeter* (1948) stresses the possible influence of the two blood streams in the division of the cono-truncus. *Patten*, *Kramer & Barry* (1948) agree with *Bremer* that the spiraling blood streams may have a molding effect on the gelatinous reticulum, leading the course of its growth into septa. This slack-water theory of septation was mentioned by *Spitzer* (1919) and *Beneke* (1920), but extended and further elaborated by *Bremer* (1931) who observed spiraling blood streams in the heart of the living chick embryo, and who studied these currents in hollow glass models of chick embryo hearts.

The idea of using glass models of hearts for the study of blood circulation is not new. *Leonardo da Vinci* (quot. *Bremer*, 1931) was probably the first to suggest this mode of approach. Valuable information on the course of blood currents within the developing heart has been obtained since *Bremer* in 1931 introduced the method in actual practice (*Romhányi*, 1952; *Kl. Goerttler*, 1954 and 1955). In brief, there is evidence of spiraling currents of blood that do not mix and that exist before septation is accomplished, or even started. There are areas of lessened lateral pressure ("seitendruckfreie Zonen" of *Goerttler*) between these spirals along which the future septa will grow. This is indirect evidence that blood currents play some role as causative factors, at least for the septation of the cono-truncus, and possibly for the atrio-ventricular canal. The spirally twisted streams have been recorded in motion pictures, first by *Patten* (quot. *Bremer*, 1931) and later by others (*Bremer*, 1931; *Kl. Goerttler*, 1954 and 1955).

Genetic factors and the appearance of two blood streams spiraling around each other do not seem to be the sole factors in operation during the septation of the cono-truncus. *Bremer* (1931) encountered one chick embryo

heart that showed spiral ridges in the conus despite the fact that blood entered the heart only from the right vitelline veins. Thus, there was only one blood stream traversing the heart. The explanation of this observation seems to lie in the shape of the entire cono-truncus.

Since 1938, *Doerr* has emphasized the importance of the form of the cono-truncus for the understanding of its septation, normal or abnormal. In 1955, *Doerr* (1955 a) summarized his concept of various anomalies of this region, and stressed the normal migration of the cono-truncus, the "vectorial conus torsion" ("vektorielle Bulbusdrehung") as having three components: a) migration of the conus from right to ventral, b) torsion of the truncus along its longitudinal axis, and c) angular bending ("Abknickung") of the conus from right and ventral to left and dorsal. Because of this bent form of the cono-truncus the spiraling of the blood streams is maintained in this region of the heart (*Kl. Goerttler*, 1954).

The vectorial torsion of the cono-truncus is, in other words, a prerequisite for the spiraling of its blood currents. This appears to be of fundamental importance for the understanding of the growth of the truncus septum, and would serve as a tenable explanation of *Bremer's* finding of spiral ridges in the conus in the presence of only one blood stream, as noted above.

The aortic and pulmonary valves

These are initiated in the XVIIth Horizon in the form of condensations of the gelatinous reticulum (*Streeter*, 1948). These structures are not valves in the morphologic sense but apparently function with a valve-like action (*Patten, Kramer & Barry*, 1948). In the XVIIIth Horizon, when the separation of the truncus is complete, the club-shaped semilunar valves are distinguishable (*Streeter*, 1948). In the older members of this age group, the crest of the interventricular septum fuses with the truncus septum to make up the membranous part of the interventricular septum, closing it in the latter part of Horizon XVIII, when the embryo is about 37 days old (*Streeter*, 1948).

On the division of the atrio-ventricular canal

It is generally agreed that the partitioning of the atrio-ventricular canal is accomplished by fusion of three structures, the two endocardial cushions and the septum primum (e.g., *Patten*, 1953 a and b). The closure of the membranous interventricular septum is accomplished later, and does not *per se* participate in the division of the canal proper.

The early contact between the dorsal and ventral endocardial cushions of the atrio-ventricular canal is established in Horizon XVI (*Streeter, 1948*). Thus, two morphologically distinct channels are produced in this region before this occurs in the conus. The differentiation of the atrio-ventricular canal cushions into valves is, however, conspicuously later than the differentiation of the aortic and pulmonary valves. The mitral and tricuspid channels show only condensed gelatinous reticulum in Horizon XVIII when the aortic and pulmonary valves are morphologically distinct (*Streeter, 1948*), and the atrio-ventricular valves are not differentiated until later (Horizon XIX, *Streeter, 1951*).

Although differentiation of the heart generally proceeds in a cephalo-caudad direction, from the conus to the sino-atrial region, it is interesting to note that the division of the atrio-ventricular canal is accomplished before completion of the morphologic division of the cono-truncus into separate aortic and pulmonary channels. Possibly the fusion of the dorsal and ventral atrio-ventricular canal cushions facilitates the normal migration of the conus.

Doerr (1952, a and b) has pointed out the close interrelation between the cono-truncus and the atrio-ventricular canal, inasmuch as the aortic part of the cono-truncus migrates in close proximity to the right atrio-ventricular ostium. *Doerr* further maintains that the migration of the cono-truncus is responsible for the asymmetric shaping of the atrio-ventricular ostia into tricuspid right and bicuspid left. *Doerr* coins the term "conflict zone" ("Konfliktzone") for the area between the ventral aspect of the atrio-ventricular ostium and the dorsal aspect of the conus. The term conflict zone implies a region where there is normally an intimate relationship between organs or structures, and where in pathologic conditions essential developmental errors may develop. The understanding of the normal interrelations of structures in these conflict zones is essential for comprehensive grasping of malformations in these regions. The conflict zone between the conus and the atrio-ventricular region is considered by *Doerr (1952 a)* to be the Achilles heel of the normal migration of the conus.

Summary

- a) Early splenic primordia in six human embryos have been shown to be present in Horizons XV to XVII of *Streeter*, when the embryo has an estimated ovulation age of 31—36 days.
- b) The fusion of the atrio-ventricular canal cushions occurs in the XVIth

Horizon, while the complete separation of the cono-truncus is accomplished about two days later, in the XVIIth Horizon (*Streeter, 1948*).

- c) The importance of spiraling blood currents in the septation of the cono-truncus has been brought out (*Bremer; Patten, Kramer & Barry; Romhányi; Kl. Goerttler*).
- d) The shape of the cono-truncus as determining the spiralization of the blood of this part of the heart has been stressed (*Doerr*).
- e) The interrelationship between the cono-truncus and the atrio-ventricular canal in the form of a "conflict zone" is emphasized (*Doerr*).

PART II

Congenital Malformations of the Heart and Great Vessels Associated with Congenital Asplenia

A. Historical Review

Congenital malformations of the heart and great vessels coexistent with agenesis of the spleen have long been looked upon as a great rarity. In the past it was the pathologist who very occasionally encountered this combination of anomalies. The first two cases on record are those of *Martin* and *Breschet* who in 1826 described the autopsy findings of septal defects, transposition of the great arteries and agenesis of the spleen. In addition, the case of *Breschet* showed pulmonary atresia.

During the nineteenth century and the first three decades of the twentieth century, occasional reports dealt with cardiac anomalies associated with agenesis of the spleen. In 1934 *Putschar* summarized the findings in all cases, including adults, reported to that time. That author collected from the literature reports on autopsies of 22 infants and children affected with this anomaly, and added a stillborn case of his own. All these were associated with various anomalies and 20 displayed definite malformations of the heart and/or great vessels.

Putschar stresses the frequent occurrence of malformations of the heart and great vessels in cases of agenesis of the spleen. He points out the common finding of abnormal septation of the heart and the occurrence of transposition of the great arteries occasionally associated with atresia or stenosis of the pulmonary trunk. Further, *Putschar* stresses the fact that many cases show abnormal systemic and/or pulmonary venous connections. *Putschar's* main interest focuses on their association with situs inversus, and he groups the cases according to this manifestation of dysontogenesis.

On the cause of the absence of the spleen *Putschar* does not comment. He mentions the possibility that, either there was a complete agenesis, or there had been a disappearance of the splenic primordia after they had been formed. *Putschar* suggests that events leading to the malformation started in approximately the third to fourth week of embryonic life, and adds that even a later date might be considered, if one should count on a complete atrophy of the splenic primordia after they had been formed.

Among cases not mentioned by *Putschar*, reference might be made to a few. In 1927, *Garvin* gave a short description of a child with *cor biloculare*, *truncus communis*, and drainage of the pulmonary veins into the superior vena cava associated with agenesis of the spleen. In 1932, *Behr* described the findings in a 2½-year-old girl. There were dextrocardia, *cor biloculare*, transposition of the great arteries, pulmonary atresia, persistent ductus arteriosus, and agenesis of the spleen. In the same year, *Kugel* reported the autopsy findings in a 4-month-old male with dextrocardia, *cor biloculare*, pulmonary atresia, partially anomalous venous connections, symmetric liver, transposed stomach, and absence of the spleen.

Since *Putschar's* paper appeared, scattered reports have been encountered in the literature. Concerning these the reader is referred to the tables at the end of this paper where the anatomic features are summarized.

The first to review the literature after *Putschar* were *Polhemus & Schafer* (1952). These authors reported four of their own cases, and stressed, for the first time, the syndromic character of cases of cardiac malformation associated with absence of the spleen. *Polhemus & Schafer* considered an *ostium atrio-ventriculare commune* to be the common denominator of the syndrome. The four cases reported by *Polhemus & Schafer* are all very similar to those mentioned above. Thus, three showed *cor biloculare*, one of which had pulmonary atresia, and another two, pulmonary stenosis. The fourth case had an *ostium primum* with persistent atrio-ventricular canal. One of the cases showed dextrocardia, and all displayed three-lobed lungs, bilaterally.

The first two cases of agenesis of the spleen associated with congenital heart disease to be diagnosed clinically, were reported by *Gasser & Willi* (1952). The authors gave an account of the clinical, including hematologic, findings in two cyanosed infants. There was a persistently increased number of Heinz bodies in the erythrocytes of the peripheral blood. The authors made the clinical diagnosis of congenital heart disease associated with agenesis of the spleen. Their diagnoses were confirmed at autopsy. Bilocular hearts with *truncus communis* and pulmonary atresia, respectively, were found. They referred to the case reported by *Fueter* (1938) and *Töndury* (1936, same case as *Fueter's*, abdominal organs reported) and stressed the similarities between the three cases. *Gasser & Willi* suggested that an endogenous lethal factor with pleiotropic effects had been at work to cause the association of anomalies.

Subsequently, a few cases have been reported (*Adler & van Slyke*, 1953; *Boys & Reed*, 2 cases, 1953; *Campbell & Forgacs*, 1953; *Campbell et al.*, 2 cases, 1953; *Baumann*, 2 cases, 1954; *Bush & Ainger*, 1955; *Willi & Gasser*,

Case 4, 1955). The two cases reported by *Campbell et al.* (1953) and Case 9 of *Campbell & Forgaçs* (1953) are remarkable as they are the oldest ever found, being 4, 8, and 5 years of age at the time of death, respectively.

For further details concerning the above-mentioned cases the reader is referred to the tables at the end of the paper.

B. Material

The material consists of 69 cases. Fifty-five have been collected from the literature, and 14 new cases have been added. Only reports with autopsy findings have been included.

Sixty-five cases show recorded anomalies in the cono-truncus region. As the purpose of this paper is to analyze the pathogenesis of malformations of the cono-truncus area of the heart, for practical purposes all cases have been grouped according to the various malformations of that region. Thus,

Type A represents cases of agenesis of the spleen with persistent truncus arteriosus;

Type B, cases of agenesis of the spleen with pulmonary stenosis or atresia, with or without transposition of the great arteries;

Type C, cases of agenesis of the spleen with transposition of the great arteries without pulmonary stenosis or atresia, and

Type D, cases of agenesis of the spleen without reported anomalies in the cono-truncus region.

The types have been chosen in this order in an attempt to cover the cases in an ontogenetic order of development. Hence, cases belonging to Type A represent more primitive forms than those of type B; i.e., embryologically, the development of the cono-truncus is assumed to have been disturbed earlier in Type A.

Type A. Cases of agenesis of the spleen with persistent truncus arteriosus

Definition. In this paper, a persistent truncus arteriosus is defined as the only artery leaving the ventricular portion of the heart without remnants, factual or implied, of any other arterial vessel. From this common artery emerge the coronary arteries, the branches of the arch and the pulmonary arterial supply (pulmonary or bronchial arteries, but not a ductus arteriosus). Thus, the definition of *Edwards* (1953 a) is followed. The material does not permit an ontogenetically adequate classification into "ideal truncus" of *Humphreys* (1932), or into aortic or pulmonic "pseudo-truncus" of *Doerr* (1955 b).

Material. Ten cases show this anomaly. Six cases have been collected from the literature (*Krausse*, case 2, 1905; *Garvin*, 1927; *Kimura*, 1930; *Shapiro*,

1930; *Gasser & Willi*, case 1, 1952; and *Baumann*, case 1, 1954). For details concerning these cases, see Table A at the end of the paper.

The author adds four cases: Nos. 1, 2, 3, and 10. The case reports are found at the end of this section.

Type B. Cases of agenesis of the spleen with pulmonary stenosis or atresia, with or without transposition of the great arteries

Definition. The pulmonary stenosis may be valvular or infundibular. Atresia denotes that the pulmonary trunk ends blindly in the myocardium from above, or that it is converted into a fibrotic strand of tissue without a lumen.

Transposition of the great arteries denotes an abnormal relationship to each other of the arterial trunks at their respective points of origin in the heart.

Material. Thirty-four cases from the literature and seven new cases belong to this type. Six cases show stenosis without transposition (*Krausse*, case 1, 1905; *Feldmann*, 1930; *Polhemus & Schafer*, cases 1 and 2, 1952; *Boggs & Reed*, case 2, 1953; *Author*, case 7).

Thirteen cases show transposition in addition to stenosis (*Kundrat*, 1887; *Gardère*, 1908; *Hu*, 1929; *Behr*, 1932; *Conn, Clark & Kissane*, case 4, 1950; *Lüdin*, 1952; *Polhemus & Schafer*, case 3, 1952; *Campbell, Reynolds & Trounce*, 2 cases, 1953; *Campbell & Forgacs*, case 9, 1953; *Author*, cases 4, 13, and 14).

Twenty-two cases display atresia of the pulmonary trunk (*Breschet*, 1826; *Arnold*, 1868; *Rokitansky*, case 1, 1875; *Geipel*, 1899; *Kugel*, 1932; *Gerstenberger*, 1938; *Lightner*, 1939; *Durie & Wyndham*, case 1, 1942; *Roszman*, 1942; *Young*, 1947; *Weinberg & Kolson*, 1949; *Leikin*, 1951; *Polhemus & Schafer*, case 4, 1952; *Gasser & Willi*, case 2, 1952; *Adler & van Slyke*, 1953; *Boggs & Reed*, case 1, 1953; *Baumann*, case 2, 1954; *Bush & Ainger*, 1955; *Willi & Gasser*, case 4, 1955; *Author*, cases 6, 9, and 12).

Thus the author contributes seven cases of this type: Nos. 4, 6, 7, 9, 12, 13, and 14. The case reports are found at the end of this section.

Type C. Cases of agenesis of the spleen with transposition of the great arteries without pulmonary stenosis or atresia

Definition. Transposition is taken in its widest sense, denoting any abnormality in the relationship in position between the arterial trunks at their points of origin in the heart. Subdivision into groups of more or less complete transposition, or corrected transposition, has not been made.

Material. Fourteen cases show this pattern. Eleven cases have been found in the literature (*Martin*, 1826; *Epstein*, 1886; *Kundrat*, 1888; *Lawrence & Nabarro*, 1901; *Mönckeberg*, 1915; *Pernkopf*, cases 4 and 5, 1926; *Fuetter*, 1938—the same case also reported by *Töndury*, 1936; *Taussig*, 1939; *Dowie & Wyndham*, case 2, 1942; *Jaccard*, case 1, 1951).

The writer adds three cases: Nos. 5, 8, and 11. The case reports are found at the end of this section.

Type D. Cases of agenesis of the spleen without reported anomalies in the cono-truncus region

Definition. In the case reports the truncus region has either been reported to be normal, or no description of this area is included in the reports accessible to the author.

Material. Four cases have been classified in this group. The author does not add any case.

Valleix's (1834) original case report has not been accessible to the writer. According to *Putschar* (1934) there was situs inversus of the heart, but no further description is given of the large arteries. This could mean that there was transposition of the great arteries; but, as not detailed description is available, by definition the case has to be grouped into this category.

Another case was reported by *Birch-Hirschfeld* (1871). This author specifically states that the great arteries are normal.

In *Bossert & Leichtentritt's* (1920) survey of bacteriologic findings in infants with various infections, one case of meningitis in a 9-month-old child (sex not given) is mentioned briefly (p. 182). At autopsy, absence of the cardiac septa with a suggestion of a four-chambered heart was found. The great arteries are not mentioned in this short report.

McLean & Craig (1922) state that the great arteries are normal in their case, a 3-month-old male with septal defects and inversion of the sino-atrial region.

Thus, in the literature there are at least two cases without anomalies of the cono-truncus region (*Birch-Hirschfeld*, 1871; *McLean & Craig*, 1922). Two other cases (*Valleix*, 1834; *Bossert & Leichtentritt*, 1920) are uncertain.

Case reports

In the following case reports the emphasis is laid on the gross pathology of the heart and great vessels. Only exceptional histologic data will be presented, and the cause of death in each instance will not be discussed. As the hearts were largely preserved for future study, routine sections were

not taken, for example, from atretic pulmonary valves. Only a minimum of clinical data will be included. The cases have been numbered according to age, and the Boston Children's Hospital cases (C.H.) are intermingled with other cases from various sources.

1. Type A

Four new cases belong to this category: Nos. 1, 2, 3, and 10.

Case 1

(Sabbatsbergs Sjukhus, O. 100/54). Stillborn. Uneventful pregnancy. The fetus was known to have been dead two weeks prior to delivery. Birth weight, 1,520 grams; body length, 43 cms.

Autopsy. Peritoneal cavity. The liver was symmetric, the left lobe equaling the right in size and occupying the left upper quadrant. The gall bladder was in the midline. The stomach was to the left of the midline. The spleen was absent. *Heart, lungs and great vessels.* The heart was of normal size, and the apex was pointing to the left. The heart was globular in shape. The lungs were composed of three lobes each. The inferior vena cava entered the right atrium, as did the superior vena cava. There were two right pulmonary veins entering the right atrium, and two left pulmonary veins that entered the left atrium. The coronary sinus opened into the right atrium. For practical purposes there was a single atrium with a rudimentary posterior septum. There was a common atrio-ventricular ostium with four cusps. The ventricular septum was absent. The only arterial vessel leaving the common ventricle was the aorta, which had three well formed leaflets. It arched over the left bronchus and gave off normal branches to the arms and the head. The last two branches of the arch consisted of two enlarged bronchial arteries, one to each lung, and leaving the aorta in its descending portion. There was no remnant of a pulmonary trunk, nor was there any evidence of a ductus arteriosus. Thus, there was a persistent truncus arteriosus (Type 4, Edwards, 1953 a). The coronary arteries were normal.

Anatomic diagnoses: Cor biloculare; levocardia; 4-cuspid A-V valve; persistent truncus arteriosus, with bronchial artery supply to lungs; anomalous pulmonary venous connection, partial, the right pulmonary veins connected to the right atrium; trilobed lungs; symmetric liver; agenesis of spleen.

An *embryologic interpretation* (Doerr, 1955 b) of the truncus in this case would be: Agenesis of the pulmonary trunk with bronchial artery supply to the lungs.

Case 2

L.C. (C.H. A-50-87). 3-day-old white male infant, the product of an uneventful pregnancy, labor and delivery. Cyanosis and respiratory distress developed on the second day of life, following attempts at feeding with water. The infant was admitted with a diagnosis of tracheo-esophageal fistula. The patient died 30 hours after admission at the age of 3 days.

Clinical impression: Question of intracranial hemorrhage; question of congenital heart disease.

Autopsy. Peritoneal cavity. There was partial situs inversus of the abdominal organs. The stomach was found in the right upper quadrant with the great curvature to the right and the pyloro-duodenal junction to the left. The duodenum, the head of the pancreas and the foramen of Winslow were in the left upper quadrant. The liver was symmetric, the left lobe equaling the right in size. The gall bladder was found in the left lobe. The spleen was absent. The cecum and the appendix were in the right upper quadrant and the segment of the colon between the right and left flexures was redundant. The inferior vena cava was located to the left of the aorta.

Heart, lungs, and great vessels. There was levocardia and the lungs had three lobes each. The inferior vena cava entered the left atrium. There were two superior venae cavae and no innominate veins. The left superior vena cava entered the left atrium; the right superior vena cava, the right. The coronary sinus emptied into the right atrium. There were four pulmonary veins, all entering the left atrium. There was no evidence of a pulmonary trunk or any remnants thereof. Emerging from the ventricular portion of the heart was only one arterial vessel, furnished with three leaflets and being a truncus arteriosus arching over the right bronchus. From the distal and proximal portions of the arch two short thick arterial trunks arose, and from these, three arteries branched on each side. The most inferior artery on each side entered the lungs and constituted the pulmonary arterial blood supply. The middle arteries were subclavian arteries and coursed to the arms while the most superior branches were common carotid arteries. Thus, the branches of the arch divided symmetrically. The interatrial septum showed an ovoid defect in its lower, anterior portion, measuring 2×1.5 cms., and constituting a persistent ostium primum. Above this there was a small interatrial septal defect in the area of the foramen ovale, but without any valve. There was no interventricular septum, nor any evidence of a rudimentary ventricle. The common ventricle communicated with the atria by way of a common 4-cuspid atrio-ventricular valve, measuring 5 cms. in circumference. The cusps were somewhat asymmetrically placed; one, posterior and in the midline;

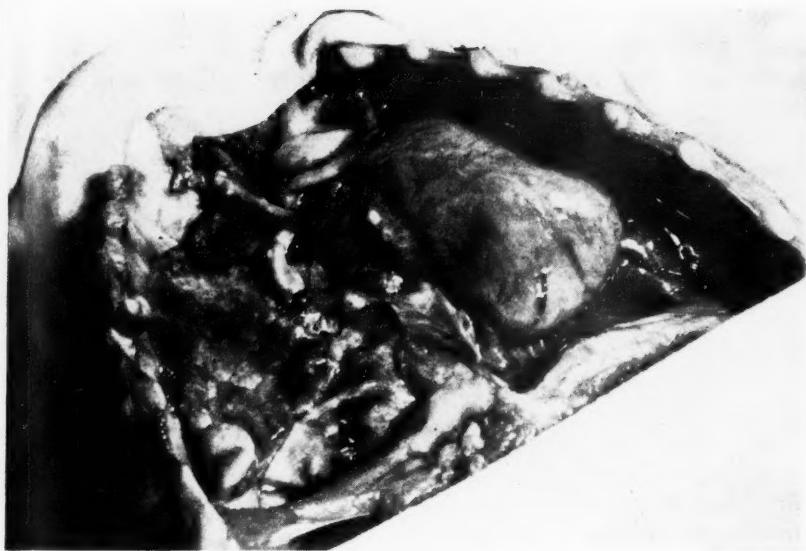


Fig. 17. Case 2. In situ picture showing a persistent truncus arteriosus with the dilated right bronchial artery branching from the descending portion of the truncus. The right superior vena cava is seen anterior to the right bronchial artery.

one, on the left; and two, on the right. They were all translucent, without cleavage, and with sharply defined margins. The circumference of the valve of the truncus measured 2.5 cms. There were two coronary arteries, one taking its origin from behind the posterior and another from behind the right anterior leaflet. Their pattern was normal.

Anatomic diagnoses: Cor triloculare biventriculare with persistent ostium primum; interatrial septal defect, small; levocardia; 4-cuspid A—V valve; persistent truncus arteriosus, 3-cuspid, with bronchial artery blood supply to the lungs; symmetric branching of the right aortic arch; anomalous systemic venous connection, partial, inferior and left superior venae cavae entering left atrium; partial abdominal situs inversus with incompletely rotated bowel, dextroposition of stomach; symmetric liver; agenesis of spleen; trilobed lungs.

An embryologic interpretation of the truncus arteriosus of this case according to *Doerr* (1955 b) would be: Agenesis of the pulmonary trunk with double ductus arteriosus.

Case 3

S.F. (C.H. A-48-270). 4-week-old white female infant with intermittent cyanosis and dyspnea that appeared 6-8 hours after birth. On admission at the age of 4 weeks there was edema of the legs and hepatomegaly, together with episodes of cyanosis. During one of these attacks the patient expired a few days after admission, at the age of 4 weeks.

Clinical impression: Tetralogy of Fallot with right aortic arch.

Autopsy. Peritoneal cavity. The liver was symmetric, the left equaling the right lobe; the gall bladder was in the left lobe. The stomach was on the left. There was a common mesentery. The cecum and appendix were in the right lower quadrant. The spleen was absent. The pancreas was annular. *Heart, lungs and great vessels.* The heart was shifted to the right although the apex pointed to the left. The lobation of the lungs was normal. The heart-lung preparation was used for an injection study and then digested. The following data are evident from the protocol. The inferior and superior vanae cavae entered the right atrium. There was no left superior vena cava. The veins draining the left lung were connected to the left atrium and those draining the right lung, connected to the right atrium. The pulmonary trunk was absent and only one arterial vessel emerged from the heart. There was a left aortic arch with normal branching. From the descending aorta two large bronchial arteries coursed, one to each lung. There was no ductus arteriosus. The right atrium was larger than the left. There were two bicuspid atrio-ventricular valves, the right measuring 4.5 and the left, 5.0 cms. in circumference. There was no interventricular septum. The truncus arteriosus was guarded by three leaflets, two of which were posterior. Two coronary arteries emerged from behind the anterior and left posterior leaflets, respectively. They branched normally.

Anatomic diagnoses: Cor triloculare biastriatum; levocardia with a shift to the right; two bicuspid A-V valves; persistent truncus arteriosus (Type 4, Edwards, 1953 a); anomalous pulmonary venous connection, partial, the right pulmonary veins entering the right atrium; symmetric liver; common mesentery; agenesis of the spleen; otitis media, purulent, left.

An attempted *embryologic interpretation* (Doerr, 1955 b) of the truncus arteriosus in this case would be: Agenesis of the pulmonary trunk with bronchial artery supply to the lungs.

Case 10

A.C. (C.H. A-27-72). This 5-month-old white male was born 1 month prematurely after an uneventful pregnancy. The infant was born cyanotic, and the cyanosis was intermittent and more prominent on crying and cough-

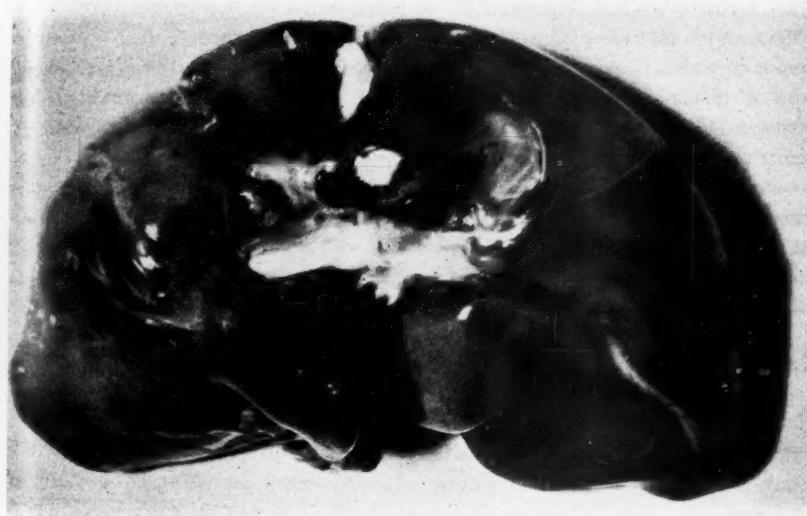


Fig. 18. Case 3. Symmetric liver, the left lobe equaling the right, with the former containing the gall bladder impression.

ing. At the age of 5 months he suddenly grew more cyanotic. On admission he was febrile and a roentgenologic examination revealed a malposition of the large bowel with signs of obstruction. The child expired shortly after an abdominal operation at the age of 5 months.

Clinical impression: Malrotation of large bowel; congenital heart disease.

Autopsy. Peritoneal cavity. The liver was transposed to the left; the stomach and the pancreas, to the right. There was a common mesentery running slightly obliquely from the upper right to the lower left quadrant. The spleen was absent. The left kidney was smaller than the right. There were post-operative adhesions surrounding an ileostomy. *Heart, lungs and great vessels.* There was dextrocardia, the apex pointing to the right. The lungs showed three lobes each with incomplete separation. The inferior and superior venae cavae and the coronary sinus entered the right side of the atrium. The right pulmonary veins were connected to the right, and the left pulmonary veins were connected to the left side of the atrium. There was only one artery leaving the ventricular portion, arching over the left bronchus and giving off the normal branches and furnishing the lungs with two large arteries from the descending portion. There was no remnant of a pulmonary trunk, nor

was there any ductus arteriosus. Thus, there was a Type 4 truncus arteriosus (*Edwards*, 1953 a). The interatrial septum was deficient, and the only remnant was a thin muscular band incompletely separating the atria. There was a bicuspid common atrio-ventricular valve and no interventricular septum. The truncus arteriosus emerged from the middle of this common ventricular cavity.

Anatomic diagnoses: Cor biloculare; dextrocardia; bicuspid common A-V valve; persistent truncus arteriosus (Type 4, *Edwards*, 1953 a); anomalous pulmonary venous connection, partial, the right pulmonary veins connected to the right atrium; abdominal situs inversus; common mesentery; agenesis of the spleen; hypoplasia of left kidney; trilobed lungs.

An embryologic interpretation of the truncus arteriosus in this case (*Doerr*, 1955 b) would be: Agenesis of the pulmonary trunk with bronchial artery supply of lungs.

2. Type B

Seven new cases belong to this category: Nos. 4, 6, 7, 9, 12, 13, and 14.

Case 4

P.A.B. (C.H. A-51-92). 1-month-old white female infant, the product of an uneventful pregnancy, labor and delivery. Shortly after birth cyanosis appeared. The cyanosis persisted in oxygen and progressed. At the age of one month she developed rapid respirations and more severe cyanosis and expired after a temporary improvement.

Autopsy. Peritoneal cavity. There was partial situs inversus of the abdominal organs with the stomach in the right upper quadrant with the great curvature lying laterally. The liver was symmetric, the left lobe equaling the right. The gall bladder was in the midline. The spleen was absent. There was a common mesentery running obliquely from the right upper to the left lower quadrant. The pancreas was freely mobile in the cavity with the tail along the lesser curvature of the stomach. *Heart, lungs and great vessels.* There was levocardia with a small, conically shaped heart. Each lung had three lobes. The inferior and superior venae cavae entered the right atrium. The pulmonary veins formed a common trunk that entered the superior vena cava. There was a valvular pulmonary stenosis, the valvular circumference measuring 1.3 cms. The pulmonary arteries were otherwise unremarkable and there was no ductus arteriosus. There was a right aortic arch with reversal of the great artery pattern. The right atrium was separated from the left only by a small crescentic band riding over a common atrio-

ventricular ostium measuring 4.5 cms. in circumference and furnished with four cusps. These were thin and translucent, but contained small firm nodules along the lines of closure. There was no interventricular septum, nor any rudimentary ventricle. The aorta arose from the common ventricle to the right of and somewhat anteriorly to the narrow pulmonary trunk. The aortic valve contained three leaflets and measured 3.2 cms. in circumference. The coronary distribution was normal.

Anatomic diagnoses: Cor biloculare; levocardia; right aortic arch; 4-cuspid common A-V valve; pulmonary stenosis, valvular; transposition of the great arteries; anomalous pulmonary venous connection, complete, to the superior vena cava; common mesentery; symmetric liver; dextroposition of stomach and pancreas; agenesis of the spleen; trilobed lungs.

Case 6

E.P. (C.H. A-46-58). 15-week-old female infant with cyanosis since birth. At 2 weeks of age dextrocardia with situs solitus of viscera was demonstrated. The cyanosis, which persisted, became more severe after a short period of improvement, and the patient died while en route to the hospital at the age of 15 weeks.

Clinical impression: Dextrocardia.

Autopsy. Peritoneal cavity. The liver was symmetric and the gall bladder was found to the left of the midline. There was a common mesentery furnishing the small bowel and the ascending and transverse portion of the large bowel. The great omentum was absent. The stomach was in the left upper quadrant. The spleen was absent. *Heart, lungs and great vessels.* There was dextrocardia, the apex of the heart pointing to the right. The lungs had three lobes each. The inferior vena cava entered the right atrium normally. Unfortunately, the superior vena cava was not dissected. The pulmonary veins all joined to form a common trunk that coursed parallel to the esophagus and pierced the diaphragm to join the portal vein. The pulmonary trunk was represented by a small thin thread of tissue lying to the left of and behind the aorta. It ended as a blind pouch in the myocardium; thus, there was pulmonary atresia. There was a right patent ductus arteriosus running in front of the trachea. There was a right aortic arch and right descending aorta. The branches of the arch were the mirror image of normal with a left innominate artery as its first branch. The right atrium was larger than the left; and in the lower, anterior portion of the interatrial septum there was a large crescentic defect constituting a persistent ostium primum.

There was a common atrio-ventricular ostium furnished with four cusps and measuring 3.3 cms. in circumference. The cusps did not show any cleavage. There was a common ventricle with a moderately prominent crista supra-ventricularis. The ventricular wall measured 0.8 cm. in thickness. The aorta arose from the center of this cavity and the valvular circumference was 2.7 cms. The coronary arteries were normal. The left atrium was small and received no pulmonary veins.

Anatomic diagnoses: Cor triloculare biventriculatum; dextrocardia; persistent ostium primum; 4-cuspid common A-V valve; pulmonary atresia with transposition of the great arteries; right aortic arch and right descending aorta; patent right ductus arteriosus; anomalous pulmonary venous connection, complete, to portal vein; common mesentery; symmetric liver; agenesis of the spleen; trilobed lungs; bronchopneumonia, acute, hemorrhagic.

Case 7

M.J.S. (Walter Reed Army Hospital, A-5779). This 4-month-old white male was the product of an uneventful pregnancy and delivery at full term. He was cyanotic at birth. Gradually, episodes of respiratory distress appeared following feeding. During one of these episodes the child expired at the age of 3 months and 25 days.

Clinical impression: Congenital heart disease, incompletely diagnosed.

Autopsy. Peritoneal cavity. The liver extended to the left flank and was enlarged, weighing 229 grams. The gall bladder was absent, but the bile ducts were normal. The stomach was in the right upper quadrant and the cardia was located to the right of the vertebral column. The pancreas was resting on the anterior aspect of the stomach wall, and attached to a rudimentary omentum. The bowel was normal in appearance. The spleen was absent. *Heart, lungs and great vessels.* The heart was globular and the apex pointed to the left. The lungs showed normal lobation. The inferior and superior venae cavae entered the right atrium and the pulmonary veins all entered the left atrium. There was a left aortic arch with normal branching. The ductus arteriosus was obliterated. The interatrial septum was deficient in its upper posterior portion, showing a widely dilated foramen ovale with a totally inadequate valve. The common atrio-ventricular valve had three atrophic cusps, and measured 5.0 cms. in circumference. There was a common ventricle without evidence of rudimentary cavities and without a septum. There was an infundibular pulmonary stenosis, 0.9 cm. in circumference. The aortic valve measured 1.4 cms. in circumference and had three normal leaflets. The coronary arteries were normal.

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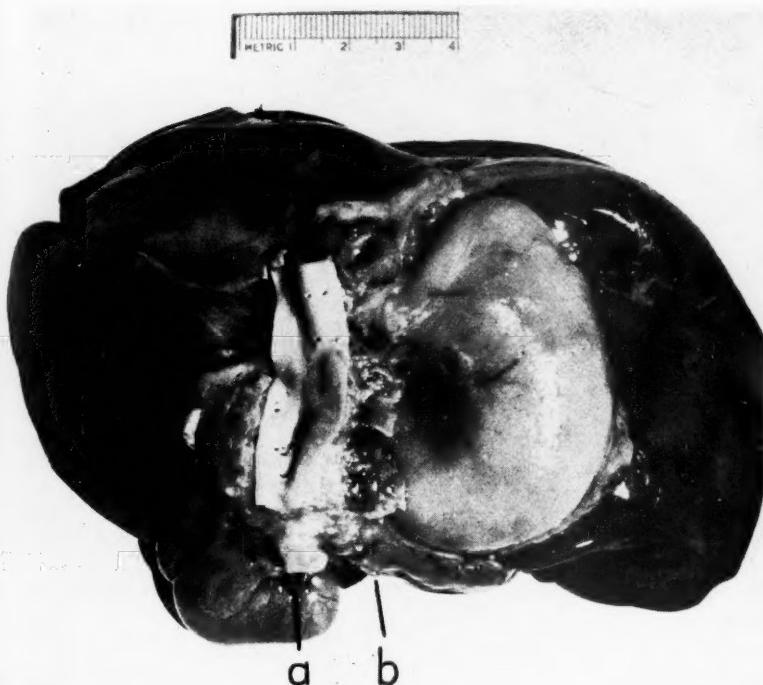


Fig. 19. Case 9. Symmetric liver, the left lobe equaling the right. The stomach is dextroposed. At (a), see accessory liver; at (b), see tip of the gall bladder. Along the greater curvature of the stomach, extending to (a), is the pancreas.

Anatomic diagnoses. Cor triloculare biventriculatum; levocardia; foramen ovale, widely patent; tricuspid, common A-V valve; pulmonary stenosis, infundibular; symmetric liver; dextroposition of stomach; absence of gall bladder; agenesis of the spleen.

Case 9

J.C. (C.H. A-53—267). 4-month-old male with cyanosis since birth. The cyanosis persisted and the patient was admitted for evaluation of its cause. During hospital stay the cyanosis increased and the patient expired at the age of 4 months.

Clinical impression: Tetralogy of Fallot, extreme, with right aortic arch.

Autopsy. Peritoneal cavity. The liver was symmetric, with the gall bladder

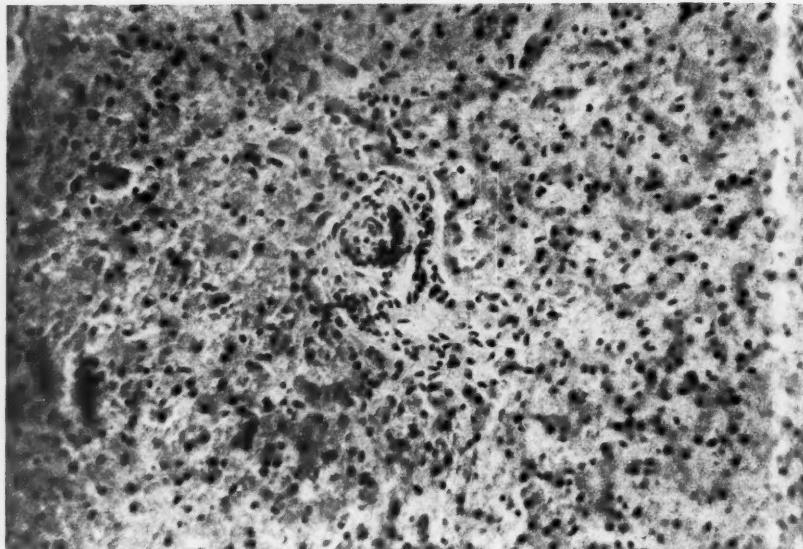


Fig. 20. Case 9. Section of accessory liver, thought on gross examination to be a spleen. x136.

in the right lobe. The stomach was transposed to the right upper quadrant, as was the pancreas. There was an accessory liver, measuring a few millimeters in diameter, attached to the posterior aspect of the duodenum on the right side, and adjacent to the gall bladder (Fig. 19). This accessory liver was misinterpreted, on gross examination, as a transposed rudimentary spleen. Histologically (Fig. 20), however, it consisted of liver tissue. There was a common mesentery running from the upper right to the lower left quadrant. *Heart, lungs and great vessels.* There was levocardia. The lungs had three lobes each. The inferior and superior venae cavae and the coronary sinus entered the right atrium; the pulmonary veins, the left atrium. There was pulmonary atresia with a transposed thread-like remnant of the pulmonary trunk ending blindly in the myocardium and situated to the left of the aorta (Fig. 21). There was a right aortic arch and a patent left ductus arteriosus. The right atrium was dilated. The interatrial septum showed a fenestration with four holes in the area of the foramen ovale, and a large defect in the lower anterior portion constituting an ostium primum. The interatrial septum arched over a common atrio-ventricular ostium that was guarded by four cusps without clefts. The cusps were confluent

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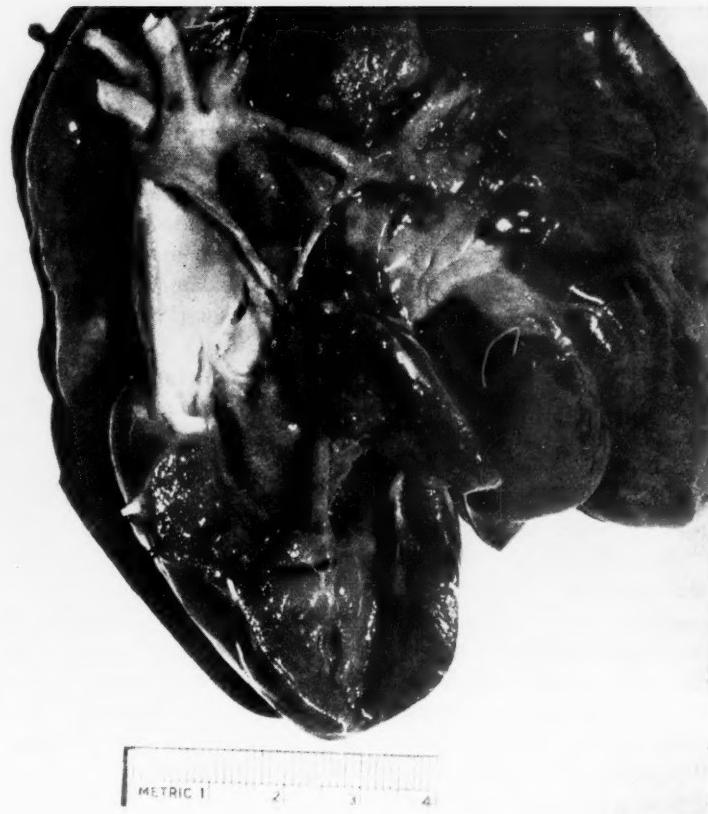


Fig. 21. Case 9. The heart, presenting the lower left ventricle and the upper portion of the right ventricle with the transposed aorta. The atretic pulmonary trunk is seen to the right of the aorta. There is a left ductus arteriosus arching over the right pulmonary artery to connect with the left pulmonary artery. The large interventricular septal defect is clearly seen.

through an interventricular septal defect encompassing the upper half of the septum. The cusps were attached to one group of papillary muscles on the lateral wall of each ventricle. From the anterior and upper aspect of the rudimentary interventricular septum, a 3 mm. thick muscular band coursed posteriorly and cephalad to insert to the left of and below the aortic outflow tract. This band traversed the ventricular cavity anteriorly to the anterior cusp of the common atrioventricular valve. The aorta

was transposed into the right ventricle; it showed three well formed leaflets and measured 3.0 cms. in circumference at the level of the valve. Two normal coronary arteries were found. In the thick wall of the right ventricle was a crista supraventricularis.

Anatomic diagnoses: Levocardia; persistent ostium primum; 4-cuspid common A-V valve; persistent foramen ovale with fenestrated valve; transposition of great arteries; pulmonary atresia; interventricular septal defect, membranous; patent ductus arteriosus; right aortic arch; symmetric liver; common mesentery; dextroposition of stomach and pancreas; accessory liver, rudimentary; agenesis of the spleen; trilobed lungs.

Case 12

D.L. (C.H. A-30—208). 9-month-old male born at full term after an uneventful pregnancy and delivery. At birth the color was dusky and, shortly afterwards, the infant developed intense cyanosis on crying. He had difficulties in feeding and often had upper respiratory infections. At the age of 3 months congenital heart disease was diagnosed. Frequent attacks of cyanosis developed and at the age of 9 months the child expired in respiratory distress.

Clinical impression: Congenital heart disease.

Autopsy. Peritoneal cavity. The larger lobe of the liver was in the left upper quadrant; the stomach was transposed to the right together with the pancreas. There was a common mesentery running from the right upper to the left lower quadrant and the cecum was in the upper right quadrant. There was no spleen. *Heart, lungs and great vessels.* There was levocardia. The lungs showed three lobes each. The inferior vena cava and a persistent left superior vena cava entered the left atrium. The right superior vena cava entered the right atrium. There was a right hepatic vein entering the right atrium. Only two pulmonary veins, one from each side, were present. They joined and were connected to the azygos vein that drained into the right superior vena cava. There was a left aortic arch with normal branching, except for the left vertebral artery that branched directly from the aorta as its third artery. The lungs received blood from two enlarged bronchial arteries emerging from the descending aorta. The hypoplastic pulmonary trunk ended blindly in the myocardium to the left of the aorta. Thus, there was pulmonary atresia. This pulmonary trunk's two main branches were hypoplastic, but contained lumens. No ductus arteriosus was present. The interatrial septum contained a widened foramen ovale measuring 0.4 cm. in diameter, and in addition there was a large defect in its lower anterior portion constituting an ostium primum. The

interatrial septum arched over a common atrio-ventricular ostium guarded by two cusps and measuring 5.5 cms. in circumference. There was only a small posterior vestigial ridge constituting a rudimentary interventricular septum. The right part of the common ventricle had the configuration of a right ventricle. The aortic outlet had three normal leaflets and the coronary arteries were normal. The lungs showed bronchopneumonia and congestion. *Anatomic diagnoses:* Cor triloculare biventriculatum; levocardia; persistent ostium primum; widened foramen ovale, small; bicuspid common A-V ostium; transposition of the great arteries; pulmonary atresia; bronchial artery blood supply to lungs; anomalous pulmonary venous connection, complete, common pulmonary vein connected to azygos vein; anomalous systematic venous connections, partial, inferior and left superior venae cavae connected to left atrium; situs inversus of abdominal viscera; common mesentery; agenesis of spleen; trilobed lungs; bronchopneumonia, acute, hemorrhagic.

Case 13

J.E.N. (Karolinska Sjukhuset B.O. 15/51). 10-month-old white male with cyanosis since birth. There was slight dyspnea. Roentgenologic examination shortly before death revealed a picture suggestive of a Tetralogy of Fallot and a common mesentery.

Clinical impression: Tetralogy of Fallot.

Autopsy. Peritoneal cavity. Liver symmetric, the left lobe equaling the right in size. The stomach was transposed to the right. There was a common mesentery. The spleen was absent. *Heart, lungs and great vessels.* Levocardia. Lobation of lungs appeared normal. The inferior vena cava and a left superior vena cava entered the left atrium. The right superior vena cava and a hepatic vein entered the right atrium. The pulmonary veins were connected to the right superior vena cava without formation of a common trunk. The right superior vena cava was partially thrombosced. The valve of the foramen ovale was fenestrated. In the lower and anterior portion the interatrial septum showed an ostium primum, and the septum arched as a crescent over a common 4-cuspid atrio-ventricular ostium the cusps of which were irregular. There was an interventricular septal defect in the membranous portion, measuring approximately 1.5 cms. in diameter. The pulmonary trunk was transposed into the left ventricle, lying to the left of the aorta and markedly stenotic but not atretic, the stenosis being valvular. There was a left aortic arch, branching symmetrically, with two innominate arteries giving off their usual branches. The ductus arteriosus was closed. The coronary pattern was normal. In addition there was a left purulent otitis and a diffuse purulent meningitis.

Anatomic diagnoses: Levocardia; persistent ostium primum; fenestrated valve of the foramen ovale; 4-cuspid common A-V valve; transposition of the great arteries; pulmonary stenosis; interventricular septal defect, membranous; anomalous systemic venous connection, partial, persistent left superior vena cava and inferior vena cava connected to the left atrium; anomalous pulmonary venous connection, total, to right superior vena cava; otitis media, left; purulent meningitis; symmetric liver; dextroposition of stomach; common mesentery; agenesis of spleen.

Case 14

C.F. (C.H. A-41-173). $2\frac{1}{3}$ -year-old white female with dextrocardia and cyanotic heart disease diagnosed at the age of 2 months. She had episodes of intermittent cyanosis since early infancy and gradually developed clubbing. At the age of 2 years episodes of severe cyanosis, loss of speech, dyspnea and facial paralysis developed. During one of these attacks she expired at the age of $2\frac{1}{3}$ years.

Clinical impression: Congenital heart disease with dextrocardia.

Autopsy. Peritoneal cavity. The liver was symmetric with the gall bladder 2 cms. to the left of the midline. The stomach was in the upper right quadrant. There was a common mesentery; the descending colon, however, was fixed to the posterior abdominal wall. The head of the pancreas was normal; the tail was along the great curvature of the stomach. There was no spleen. *Heart, lungs and great vessels.* There was dextrocardia, the apex of the heart pointing to the right. The left lung had three lobes; the right lung, two. There was inversion of the sino-atrial region, the inferior and superior venae cavae entering the left-sided atrium, while the pulmonary veins entered the right atrium. The interatrial septum contained a large defect constituting $\frac{4}{5}$ of the entire septum in its lower anterior portion. The right atrio-ventricular ostium was bicuspid; the left, tricuspid. The aorta lay anteriorly and to the left of the pulmonary trunk that was transposed into the left-sided ventricle and was smaller than the aorta. The left-sided ventricle gave rise to the aorta and the pulmonary trunk and showed a well-developed crista supraventricularis. Thus, the ventricles were transposed. No arterial vessel emerged from the right-sided ventricle. There was a membranous interventricular septal defect measuring 1.5 cms. in diameter. The pulmonary outflow tract had two cusps and measured 0.9 cm. in diameter.

Anatomic diagnoses: Situs inversus of thoracic viscera with dextrocardia and inversion of sino-atrial region and transposition of ventricles; persistent

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ostium primum; transposition of the great arteries; pulmonary stenosis, valvular; (partial transposition in dextrocardia with hypoplasia of pulmonary trunk, *Lev*, 1953 a); interventricular septal defect, membranous; symmetric liver; dextroposition of stomach and pancreas; common mesentery; agenesis of the spleen.

3. Type C

To this category three new cases belong: Nos. 5, 8, and 11.

Case 5

M.H. (C.H. A-53—243) 2-month-old white female with cyanosis and vomiting at birth. The cyanosis persisted and signs of paracolon meningitis were found. She recovered rapidly on antibiotics. As occasional vomiting persisted, a barium swallow was performed and malrotation of the bowel was found. The liver was enlarged. Occasional vomiting persisted, and during therapy she suddenly expired at the age of 2 months.

Clinical impression: Congenital heart disease.

Autopsy. *Peritoneal cavity.* There was symmetry of the liver. The gall bladder was in the right lobe of the liver. The stomach was on the right. There was complete malrotation of the bowel with a common mesentery. The spleen was absent. *Heart, lungs and great vessels.* There was levocardia. The inferior and superior venae cavae entered the right atrium and the pulmonary veins, the left atrium. The lower anterior portion of the interatrial septum showed a large defect representing a persistent ostium primum. The foramen ovale was widened. The right-sided atrio-ventricular valve was bicuspid, while the left-sided was tricuspid, malformed with tiny cusps, and was continuous with the right atrio-ventricular valve. There was a segmental transposition of the ventricles with a left-sided hypoplastic chamber communicating with the right-sided ventricle. The right-sided ventricle had the configuration of the normal left ventricle while the left-sided one had the configuration of a normal right ventricle with a crista supraventricularis. There was an interventricular septal defect in the membranous portion. There was transposition of the great arteries, the aorta arising from the left-sided (right) ventricle, and the pulmonary trunk, slightly wider than the aorta, from the right-sided (left) ventricle posteriorly and to the right of the aorta. The aorta branched normally. There was a patent left ductus arteriosus and a coarctation of the aorta between the left common carotid artery and the left subclavian artery. Thus, there was a partially corrected transposition of the great arteries.



Fig. 22. Case 5. The heart, with the left-sided (transposed right) ventricle opened to show the trabecular pattern of the transposed right ventricle. The persistent ostium primum is clearly seen in the center of the picture.

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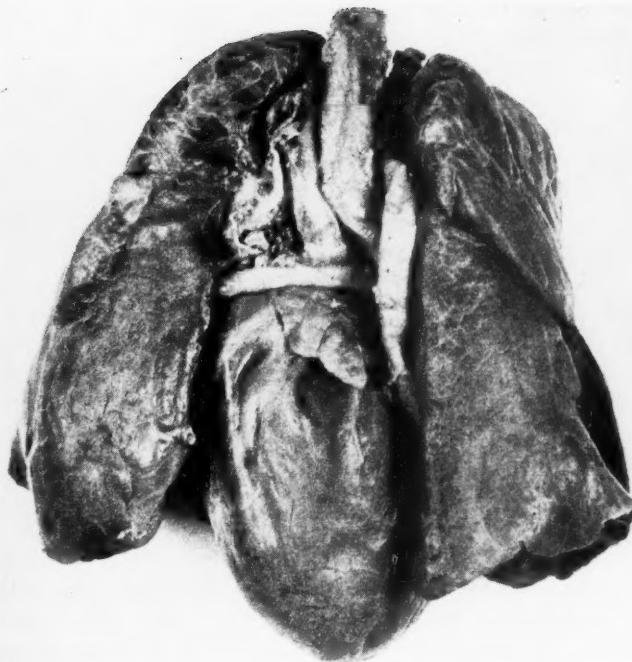


Fig. 23. Case 8. Heart-lung preparation, dorsal view. The pulmonary veins join to form a common channel seen to the left of the trachea. The aortic arch and the descending aorta are to the right of the trachea.

Anatomic diagnoses: Inversion of the sino-atrial region and segmental situs inversus of the ventricles; levocardia; persistent ostium primum; patent foramen ovale; right bicuspid and malformed left tricuspid A-V valves; complete transposition, partially corrected; interventricular septal defect, membranous; coarctation of the aorta; patent ductus arteriosus; malrotation of bowel, complete; absence of spleen; acute hemorrhagic bronchopneumonia; meningitis, healed.

Case 8

S.P. (C.H. A-41-29). 4-month-old female born at full term. At the age of 2 $\frac{1}{2}$ months she ceased to gain weight after an upper respiratory infection. At the age of 4 months she suddenly developed edema of the legs, cyanosis and dyspnea. The patient suddenly expired while in an oxygen tent.

Clinical impression: Congenital heart disease, type undetermined.

Autopsy. Peritoneal cavity. The liver was symmetric and the gall bladder was to the left of the midline. The stomach was in the left upper quadrant. There was a common mesentery and the cecum was found in the right upper quadrant. The spleen was absent. No right umbilical artery was found. *Heart, lungs and great vessels.* There was levocardia. The lungs showed abnormal lobation, the left having 4 and the right, 3 lobes. There was inversion of the sino-atrial region. The inferior vena cava and the coronary sinus entered the left atrium, and the superior vena cava, the right atrium. The left atrium contained a linea terminalis. All pulmonary veins joined and formed a common channel that was connected to the left innominate vein. This common channel was interpreted as a partially persistent left superior vena cava that had degenerated between the entrance of the pulmonary veins and the heart, thus acting as a "common pulmonary vein". The interatrial septum was deficient, the only remnant being a round median bar 1.5 cms. in length, tapering from a diameter of 0.6 to 0.3 cm. as it coursed from the postero-inferior to the antero-superior wall of the common atrium. There was a common atrio-ventricular ostium guarded by 4 cusps and measuring 2.5×3.0 cms. in greatest diameters. The ventricular septum was rudimentary and consisted of a vestigial rounded elevation in the lower anterior portion of the common ventricle. The aortic orifice was situated in front of and slightly to the right of the pulmonary outlet. It measured 0.9 cm. in diameter, while the pulmonary orifice measured 1.1 cms. in diameter. Both valves were furnished with three semilunar leaflets. There was a right aortic arch with branching the mirror image of normal. The ductus arteriosus was atretic. The coronary pattern was reversed. There were no signs of stenosis of the pulmonary orifice, neither infundibular nor valvular. *Anatomic diagnoses:* Cor biloculare; levocardia; 4-cuspid common A-V ostium; inversion of the sino-atrial region; transposition of the great arteries; right aortic arch; anomalous pulmonary venous connection, total, to partially persistent left superior vena cava ("common pulmonary vein") connected with left innominate vein; symmetric liver; common mesentery; agenesis of the spleen; abnormal lobation of lungs.

Case 11

L.S. (C.H. A-40-101). 6-month-old white male was delivered at full term and was not reported to have been cyanotic at that time. However, cyanosis gradually appeared, particularly after crying. On admission at the age of 6 months the heart and liver were enlarged. The child expired suddenly in circulatory collapse at the age of 6 months.

Fig.
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Fig. 24. Case 11. Section of accessory liver, thought on gross examination to be a spleen. $\times 136$.

Clinical impression: Congenital heart disease.

Autopsy. Peritoneal cavity. The liver was symmetric. The stomach was in the left upper quadrant. The head of the pancreas was normal, while the tail was bent forward and was located intraperitoneally between the stomach and the transverse colon. There was a common mesentery with the cecum lying in the midline. A small accessory liver measuring $3.0 \times 1.0 \times 0.1$ cms. was found to the left of the vertebral column, loosely attached to the liver. Grossly, this liver was interpreted as the spleen (cf. Case 9) but histologically it consisted of liver tissue (Fig. 24). *Heart, lungs and great vessels.* There was levocardia. The lungs had three lobes each. The inferior and superior venae cavae and the coronary sinus all entered the right atrium, as did two hepatic veins separately. There was completely anomalous venous connection inasmuch as the pulmonary veins joined the right subclavian and the right jugular veins to form the right innominate vein with drainage into the right atrium. The interatrial septum was deficient consisting of a falciform bar with a large interatrial septal defect in the upper, posterior portion and a widely patent ostium primum below. The interatrial septum arched over a common atrio-ventricular ostium guarded by four cusps without evidence

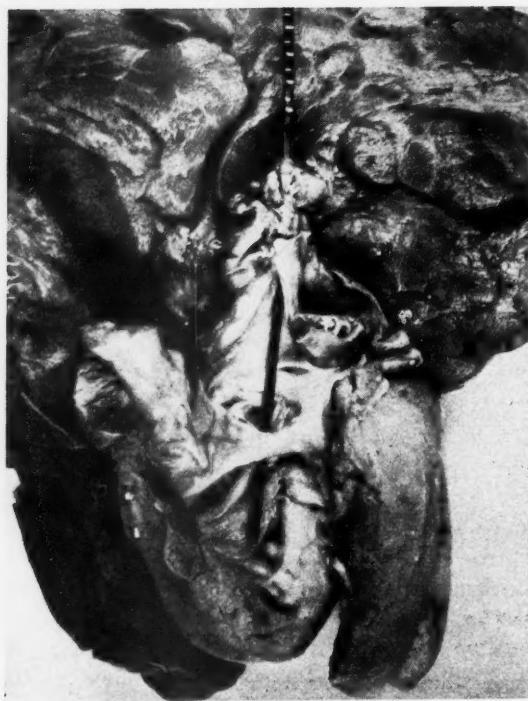


Fig. 25. Case 11. Cor biloculare. The only remnant of a septum is the falciform bar arching over the common A-V ostium. The primitive interatrial septum is seen in front of the probe.

of cleavage. The interventricular septum was absent and functionally the heart constituted a cor biloculare. The aorta arose to the right of and anteriorly to the pulmonary trunk, neither of these showing stenosis of the orifices. The ductus arteriosus was obliterated. The coronary pattern was normal.

Anatomic diagnoses: Cor biloculare; levocardia; 4-cuspid common A-V ostium; transposition of the great arteries; anomalous pulmonary venous connection, total, the pulmonary veins connected to the right jugular and right subclavian veins, forming the right innominate vein; symmetric liver; common mesentery; accessory liver, rudimentary; agenesis of the spleen; trilobed lungs; otitis media, left.

C. Survey of the Pathologic Features Displayed by Cases of Agenesis of the Spleen

It is evident from the preceding case reports and Tables A through D that there are considerable variations in the anatomic pattern of the material. Some main features that many cases have in common will be reviewed. Because of the method of selection, all show abnormalities of the heart as well as agenesis of the spleen. In addition, there are anomalies of the great arteries, as has been shown. A certain number show abnormal systemic and/or pulmonary venous connections. The lobation of the lungs is abnormal and the abdominal viscera often show varying degrees of situs inversus.

For details concerning the different anomalies, and for references, see Tables A—D at the end of the paper.

Dextrocardia

The definition by *Lichtman* (1931) is followed. Dextrocardia denotes a congenital condition in which the heart assumes a position in the right part of the thoracic cavity with the apex pointing to the right. No subdivision into *Lichtman's* three, or *Mandelstamm & Reinberg's* (1928) four, types has been attempted. Twenty-three cases display dextrocardia. Fifteen of these also show varying degrees of situs inversus.

Right aortic arch

If the arch of the aorta, or of a common truncus, crossed over the right bronchus it was designated as a right aortic arch. This was specifically stated in 25 cases; ten of these also showed dextrocardia.

Anomalies of the atrio-ventricular region

In 60 cases, descriptions of this region are available. Fifty-six cases showed an abnormal A—V region.

Most often there is a *common atrio-ventricular ostium*; 46 cases show this anomaly.

Fourteen of these are *four-cuspid* (*Krausse*, case 1, 1905; *Feldmann*, 1930; *Kugel*, 1932; *Rossman*, 1942; *Weinberg & Kolson*, 1949; *Author*, cases 1, 2, 4, 5, 6, 8, 9, 11, and 13).

Ten are *tricuspid* (*Arnold*, 1868; *Rokitansky*, 1875; *Epstein*, 1886; *Geipel*, 1899; *Shapiro*, 1930; *Leikin*, 1951; *Polhemus & Schafer*, cases 2, 3, and 4, 1952; *Author*, case 7).

Seven are *bicuspid* (*Gardère*, 1908; *Pernkopf*, case 4, 1926; *Hu*, 1929; *Campbell & Forgacs*, 1953; *Adler & van Slyke*, 1953; *Author*, cases 10 and 12).

Six are *five-cuspid* (*Behr*, 1932; *Fueter*, 1938; *Gerstenberger*, 1938; *Lichtenauer*, 1939; *Durie & Wyndham*, case 2, 1942; *Conn et al.*, 1950).

Three had *one fused cusp* (*Lüdin*, 1952; *Baumann*, 2 cases, 1954).

One had *six cusps* (*Pernkopf*, case 5, 1926).

One had practically no valvular tissue (*Krausse*, case 2, 1905).

In the remaining four of the 46 cases with common A-V ostium, the number of cusps is not reported (*Taussig*, 1939; *Polhemus & Schafer*, case 1, 1952; *Campbell et al.*, case 6, 1953; *Willi & Gasser*, case 4, 1955).

Another type of malformation of the A-V region is *mitral atresia*, as inferred from the descriptions. This is present in five cases (*Lawrence & Nabarro*, 1901; *Mönckeberg*, 1915; *Kimura*, 1930; *Durie & Wyndham*, case 1, 1942; *Campbell et al.*, 1953).

Some of these cases have not been designated as cases of mitral atresia by the authors. The reasons for classifying them here, despite this fact, will follow. *Mönckeberg* (1915) does not use the term mitral atresia, but the case of that author is beyond doubt because of the thorough examination of the heart. Because of his complete examination, *Mönckeberg's* case deserves a special comment. It concerns a cor triatriatum pseudotriiloculare with rudimentary mitral valve and left ventricle visualized only after serial sectioning of the heart. *Mönckeberg* stresses the importance of histologic examination of congenitally deformed hearts, and considers this method of examination the only procedure for achieving an exact diagnosis in many cases of complicated congenital defects.

Kimura's case is not stated to be a case of mitral atresia in the original report. From the description of the heart this is not evident, and the description is incomplete. However, the pictures show the left atrium ending blindly towards the ventricle, and the right atrium seems to have been the only atrium in direct communication with the common ventricle. The atrio-ventricular valve is described as being irregular and furnished with several irregular valvular flaps. The A-V valve was malformed and in the inadequate description of the heart mitral atresia has not been ruled out. It seems very likely, as judged from the pictures. However, *Kimura* in his report focuses his main interest on associated genital anomalies. However the case of *Kimura* is classified, it displayed an anomalous atrio-ventricular valve.

Case 3 of *Campbell et al.* is not classified as an outright case of mitral atresia in their communication. To the present author it seems highly probable that it is, and it has been classified as such here, for the following reasons.

The left atrium was rudimentary; the right was very large. The left received the common pulmonary vein and did not open into the single ventricle. The left atrium communicated with the right by way of a slit-like defect of the lower anterior interatrial septum. There was a single tricuspid A—V valve. The authors point out that the left atrium was separated from the ventricle by ventricular myocardium and not by a thin membrane. The area of a possible, rudimentary left ventricle was not stated to be histologically examined. The single ventricle did not show any evidence of an interventricular septum. The great arterial trunks were transposed and emerged from this single (possibly right) ventricular cavity, the pulmonary trunk being stenosed. The possibility of a mitral atresia has not been ruled out.

A third type of anomalous A—V region is *tricuspid atresia*. This is highly probable in *Young's* (1947) case of a premature that had a diminutive right ventricle, absence of tricuspid valve, and a single atrium in communication with the left ventricle only by way of a bicuspid A—V valve. The aorta was transposed into the rudimentary right ventricle. The case of *Breschet* (1826), the original of which has not been accessible to the author, has also been included in this group. *Lichtman* (1931) states that the tricuspid is vestigial.

Two bicuspid A—V valves were present in two cases (*Gasser & Willi*, case 1, 1952; *Author*, case 3).

One of the author's cases showed *transposition of the A—V valves* in levocardia (case 14).

Thus, of the 60 cases with accessible descriptions of the atrio-ventricular region, four were reported as normal (*Birch-Hirschfeld*, 1871; *McLean & Craig*, 1922; and *Boggs & Reed*, 2 cases, 1953). As for *Boggs & Reed*'s two cases, they seem highly questionable as there is no detailed description of the area concerned, nor of the cardiac septa. Nevertheless, the authors state in their summary that "atrio-ventricularis communis" is one characteristic of the "syndrome" of splenic agenesis. It seems highly probable that there were anomalies in the A—V region, although it is passed over as "not unusual" in the description. *It is noteworthy that the two first-mentioned cases belonged to Type D and showed no truncus anomalies.*

The other two cases belonging to Type D include no accessible reports on the A—V region. *Bossert & Leichtentritt's* (1920) case report includes no mention of the atrio-ventricular valves, nor of the truncus region. *Valleix's* (1834) case is accessible to the author in *Putschar's* (1934) summary only. In this summary it is stated that there was a left tricuspid valve and situs inversus of the heart. The right atrio-ventricular valve is not mentioned, nor is the truncus region.

In summing up the findings of A—V anomalies with reference to the types of truncus malformations, the following is found.

Type A includes a total of ten cases. Nine of these showed A—V anomalies, and one (*Garvin*, 1927) included no description of the area concerned.

Type B comprises 41 cases. Thirty-six of these displayed A—V anomalies, two were reported normal (*Boggs & Reed*, 1953), and three case reports included no description of the A—V region (*Kundrat*, 1887; *Gasser & Willi*, case 2, 1952; *Bush & Ainger*, 1955).

Type C contains 14 cases. Eleven of these showed A—V anomalies, and in three no description was given of the region in question in available reports (*Martin*, 1826; *Kundrat*, 1888; *Jaccard*, 1951).

Type D, finally, consists of four cases, two of which were reported to be normal (*Birch-Hirschfeld*, 1871; *McLean & Craig*, 1922), and two of which did not contain any description of the A—V region (*Valleix* 1834; *Bossert & Leichtentritt*, 1920).

Anomalies of the cono-truncus region

These have been described in Part II, Section B. Suffice it here to emphasize that 65 cases out of 69 contained data to show that this region was anomalous. Two cases were reported normal (*Birch-Hirschfeld*, 1871; *McLean & Craig*, 1922); one contained no complete description (*Valleix*, 1834); and one did not mention the region in any way (*Bossert & Leichtentritt*, 1920).

Septal defects

Varying degrees of interatrial and/or interventricular septal defects are present in all cases except two with incomplete descriptions (*Kundrat*, quot. by *Schrötter*, 1887; *Kundrat*, 1888). The anatomic variation is wide. Thus, 32 cases are examples of *cor bilobulare* with absence of septa, or with a small muscular band traversing the common atrium in a postero-inferior to antero-superior direction. Eighteen cases display an ovoid defect in the region of the *ostium primum* with an atrial septum arching over the atrioventricular ostium. There are no data concerning cleavage of the mitral leaflets. In the author's own material no case with cleft mitral valve is present; nor has it been possible to collect cases of agenesis of the spleen in case reports with true examples of this anomaly (e.g., *Rogers & Edwards*, 1948; *Curtin*, 1952; *Edwards*, 1953 a).

Occasionally, there are defects in the area of the *foramen ovale*. Ten cases with this anomaly have been collected. Among these, *Birch-Hirschfeld's* (1871) case deserves a note. *Putschar* (1934) classifies that case in a group

without cardiac anomalies. However, as *Putschar* points out, there was a more than 2-groschen large "foramen ovale" in the atrial septum. The case concerned a new-born (age "several hours", no birth-weight given) that died suddenly. As the only unusual finding in the heart, *Birch-Hirschfeld* found this more than 2-groschen large "foramen ovale". A 2-groschen ("2 Neugroschen") from Sachsen, Germany, of 1868 has a diameter of 21 mms. (*Rasmussen*, 1955). Suffice it to say that an interatrial septal defect measuring approximately 20 mms. in diameter in infancy can hardly be classified as a "foramen ovale". *Birch-Hirschfeld* points out that he was unable to close the defect by pressing the valve of the foramen ovale against the atrial septum. However, the author did not mention whether the atrial septum was deficient in its anterior lower portion; so the defect cannot be classified as a true ostium primum.

Anomalous connections of pulmonary veins

This term covers anatomic conditions in which pulmonary veins terminate in any vessel or chamber other than the left atrium (*Edwards*, 1953 b). It is to be distinguished from *anomalous drainage* which denotes abnormal blood flow from the lungs with or without abnormal termination of pulmonary veins (*Edwards, DuShane, Aleott & Burchell*, 1951; *Swan, Burchell & Wood*, 1953; *Edwards*, 1953 b). The connections can be partially or totally abnormal.

Totally anomalous pulmonary venous connections were found in 31 of the 69 cases presented. Most commonly, the pulmonary veins joined the right superior vena cava. This occurred in 12 instances (*Epstein*, 1886; *Geipel*, 1899; *Mönckeberg*, 1915; *Garvin*, 1927; *Durie & Wyndham*, case 1, 1942; *Boggs & Reed*, case 1, 1953; *Baumann*, 2 cases, 1954; *Willi & Gasser*, case 4, 1955; *Author*, cases 4, 12 and 13). In one of these the pulmonary veins drained into the azygos vein and then into the right superior vena cava (*Author*, case 12). In three other cases the veins first joined the innominate vein before draining into the right superior vena cava (*Gasser & Willi*, case 2, 1952; *Author*, cases 8 and 11). In the writer's Case 8 (Fig. 23) and in Case 2 of *Gasser & Willi* (1952) there was a "common pulmonary vein" connected with the left innominate vein. It was interpreted as a partially persistent left superior vena cava (see below, *Anomalous connections of systemic veins*, p. 62). In seven instances the pulmonary veins terminated in the right atrium (*Rokitansky*, 1875; *Krausse*, case 2, 1905; *McLean & Craig*, 1922; *Pernkopf*, case 4, 1926; *Leikin*, 1951; *Bush & Ainger*, 1955; *Author*, case 14). In no less than seven cases, a common pulmonary vein joined

the portal vein (*Arnold*, 1868; *Hu*, 1929; *Young*, 1947; *Weinberg & Kolson*, 1949; *Jaccard*, 1951; *Lüdin*, 1952; *Author*, case 6). In one case (*Boggs & Reed*, case 2, 1953) the pulmonary veins joined different systematic veins (right superior vena cava, left innominate and inferior vena cava) before draining eventually into the right atrium.

One example of *totally anomalous pulmonary venous connection with normal drainage* was found in the literature (*Gerstenberger*, 1938). This case is principally similar to that of *Becu, Tauxe, DuSchane & Edwards* (1955) with a suggestion of a *cor triatriatum*. A small sinus was formed by the joined left superior vena cava and a common pulmonary vein. The common pulmonary vein was collecting all pulmonary veins, and the sinus opened into the left atrium. In other words, the pulmonary veins were abnormally connected with a persistent left superior vena cava. As this vein terminated in the left atrium without any connection with the coronary sinus, the *drainage* was normal.

Partially anomalous pulmonary venous connections were present in five cases (*Kimura*, 1930; *Lightner*, 1939; *Author*, cases 1, 3 and 10). In every instance the anomalous connection concerned the right pulmonary veins that were connected with the right atrium. In all these cases the left pulmonary veins terminated in the left atrium; so there were symmetrically abnormal connections.

Another form of anomalous pulmonary venous connection is the *common pulmonary vein*. This denotes conditions in which pulmonary veins form a common channel. This is the case in all instances mentioned above where there was abnormal connection with the portal vein. Occasionally, a common pulmonary vein empties into the left atrium. A common pulmonary vein was present in 20 cases, in five of which it was connected with the left atrium. In each of five cases it was connected with the right superior vena cava; in seven with the portal vein; in two cases with the right atrium and in another case with the azygos vein. In Case 2 of *Boggs & Reed* (1953) a common pulmonary vein was formed by the veins of the lower lobes only. This common vein was connected with the inferior vena cava.

Anomalous connections of systemic veins

This is present in 29 instances. In addition, there are two probable cases (*Feldmann*, 1930; *Jaccard*, 1951). *Feldmann* states that the left superior vena cava emptied into the left ventricle (sic!). In *Jaccard's* case there were bilateral superior venae cavae and a common atrium, but the author does not state which part of the atrium received the left superior vena cava.

Most commonly, there is partially anomalous connection in the form of a *left superior vena cava* connected with the *left atrium*. This was the case in 27 instances, including the cases of *Feldmann*, *Jaccard*, and *five cases with inversion of the sino-atrial region* (*Arnold*, 1868; *McLean & Craig*, 1922; *Pernkopf*, case 4, 1926; *Bush & Ainger*, 1955; *Author*, case 14). In no instance is the left superior vena cava reported as draining into the coronary sinus, as is otherwise commonly the situation when this vein persists into postfetal life (Group I (A) of *McManus*, 1941; *Edwards*, 1953 a). In 19 cases there were a right and a *persistent left superior vena cava*, symmetrically connected with the right and left atria, respectively. *McManus'* (1941) classification of the various types of left superior vena cava does not include conditions in which the vein is connected with the left atrium. To the writer the term *persistent* should be reserved for cases where there are bilateral venae cavae. Thus, the following classification is proposed:

- I. Persistent left superior vena cava,
 - A) Connected with the coronary sinus
 - B) Connected with the pulmonary veins (partially persistent left superior vena cava)
 - C) Connected with the left atrium
- II. Left superior vena cava without right superior vena cava.

The term persistent left superior vena cava is retained as it is in common use. Embryologically, the correct term would be *persistent left anterior cardinal vein*. This classification is a modification of that of *McManus* (1941), with the addition of Group I (C) which is represented by 19 cases in the present material.

In the above-mentioned cases with inversion of the sino-atrial region, the *Author's* Case 8 is not included. There was a "common pulmonary vein" connected with the left innominate vein, and the anomaly is an example of Group I (B) in the above classification. It is in this respect similar to Case 4 of *Gardner & Oram* (1953). Case 2 of *Gasser & Willi* (1922) shows the same type of anomaly.

Among the 31 cases with anomalous connection of systemic veins (including the cases of *Feldmann* and *Jaccard*) there are nine cases described as having hepatic veins, separately connected with the atrium which did not receive the inferior vena cava. Of these, three had no left superior vena cava (*Rokitansky*, 1875; *Epstein*, 1886; *Young*, 1947) and have not been accounted for in the above description. The hepatic veins connected separately with the atria are interpreted as *persistent omphalomesenteric veins* (*venae rechentes hepatis*; *Mall*, 1906; *Broman*, 1921; *Mönckeberg*, 1924).

Three cases had an inferior vena cava connected with the right atrium (*Martin*, 1826; *Rokitansky*, 1875; *Epstein*, 1886), and a hepatic vein connected with the left atrium. This hepatic vein represents a *persistent left omphalomesenteric vein*. In six cases the inferior vena cava was connected with the left atrium (*Mönckeberg*, 1915; *Fueter*, 1936; *Young*, 1947; *Leikin*, 1951; *Author*, cases 12 and 13). The right hepatic vein connected with the right atrium in these cases is interpreted as a *persistent right omphalomesenteric vein*. *Bush & Ainger's* case (with inversion of the sino-atrial region) is a probable seventh case with persistence of the right omphalomesenteric vein. Angio-cardiography showed that case to have "bilateral inferior vanae cavae". This possibility is, however, not stated to be confirmed in the autopsy report.

The above-mentioned seven cases with a common pulmonary vein connected with the portal vein may be interpreted as showing persistence of an omphalomesenteric vein, as pointed out by *Weinberg & Kolson* (1949) and in *Jaccard's* (1951) paper.

In addition, there are other anomalies of the systematic veins such as *absent coronary sinus* (e.g., *Pernkopf's* 2 cases, 1926) and a left azygos vein connected with the left superior vena cava (e.g., *Durie & Wyndham*, case 2, 1942).

Abnormal lobation of lungs

This is found in 46 cases. Most commonly, there is symmetric lobation, the lungs being mirror images of each other. This is the case in 40 instances. Most often, there are three more or less complete lobes in each lung. Thirty-five cases show trilobed and four, four-lobed lungs, while in one case the lungs were five-lobed.

Anomalous abdominal viscera

By definition, the spleen is absent in all cases. The liver is often transposed to the left side, the larger lobe being situated in the left upper quadrant (17 cases); or it is symmetric, the left lobe equaling the right in size (31 cases). The stomach is transposed to the right upper quadrant in 33 cases. There is a common mesentery, more or less complete in 33 cases. In addition, there are minor anomalies of the pancreas (annular; tail transposed, etc.). In summary, the abdominal viscera show varying degrees of *situs inversus* with a tendency towards symmetry, most marked in the shape of the liver and in the attachment of the mesentery.

A note on symmetry

It is evident from the preceding descriptions of cases of cardiac malformations associated with agenesis of the spleen that the varied picture of malformations has a common pattern with a tendency towards visceral symmetry.

Thus, the *great arteries* display symmetric features. There are varying degrees of symmetric arrangement of the trunus derivatives: trunus communis, pulmonary atresia, and transposition of the arterial trunks. There is one case interpreted as persistence of double ductus arteriosus (*Author*, case 2).

The *systemic veins* may display symmetry, most often in the form of a persistent left superior vena cava, and occasionally, persistence of omphalo-mesenteric veins occurs.

The *pulmonary veins* likewise may have a symmetric pattern, with persistence of a common pulmonary vein or with the left pulmonary veins connected with the left, and the right, with the right atrium.

The *heart* may display a pattern that could be interpreted as symmetric; or bilocular with complete absence of cardiac septa is a common finding in this "syndrome of visceral symmetry".

The *abdominal organs* display symmetric arrangement in a number of cases. The liver often has a left lobe equaling the right in size and shape. There is a common mesentery in a number of cases. As has been repeatedly stressed in the literature, partial or total situs inversus is part and parcel of this tendency to symmetry (e.g., *Toldt*, 1889; *Geipel*, 1899 and 1903; *Töndury*, 1936; *Torgersen*, 1949, 1950 a and 1950 b). It is not the intention of the author to discuss the varying forms of symmetry or situs inversus that have been shown to occur in these cases (cf. *Harrison*, 1945; *Torgersen*, 1949 and 1950 b). It would be beyond the scope of this paper.

The author suggests that this syndrome should be called asplenia, a teratologic syndrome of visceral symmetry. This is in analogy with the teratologic syndromes produced by vitamin A deficiency during gestation (*Wilson* & *Warkany*, 1950 and 1953; *Warkany*, 1952/53).

On the occurrence of serious infections

Agenesis of the spleen in infancy and childhood is usually associated with severe malformations of the heart and great vessels, as is evident from this survey. Eleven cases out of the 12 with agenesis of the spleen in an autopsy series comprising 7,032 infants and children, showed associated malformations of the heart and great vessels. The twelfth case, a 9-month-old white female,

(C.H., A-25—167), showed purulent meningitis without associated anomalies of the cardiovascular system. For the latter reason, it has not been included in this study. It is mentioned in this context, however, as *King & Shumacker* (1952) have called attention to the relative frequency of infections, meningitis in particular, following splenectomy in infancy. These authors collected 15 cases in which splenectomy had been performed before the age of six months. Of these, six contracted serious infections, and three of them died. Among these, *King & Shumacker* report four cases with either meningitis or overwhelming meningococcemia. *Gross* (1953) does not have the same experience. After 58 successful splenectomies performed on children, there have been only two known deaths from severe infections, one of these being meningitis. *Gellis* (1954), in a comment on *Boggs & Reed's* abstracted paper, points out that he has encountered three cases where septicemia developed several months after splenectomy.

In the material presented here, 11 cases showed evidence of serious infections at the time of death. Of these, four had *meningitis* (*Bossert & Leichtentritt*, 1920; *Polhemus & Schafer*, case 3, 1952; *Author*, cases 5 and 13). One had ulcerative *endocarditis* of a bicuspid pulmonary valve and abscesses in the kidneys (*Gardère*, 1908). Five showed *bronchopneumonia* (*Gardère*, 1908; *McLean & Craig*, 1922; *Author*, cases 5, 6 and 12). Three had *otitis media* (*Author*, cases 3, 11 and 13). One had pulmonary *tuberculosis* (*Shapiro*, 1930). This incidence of infections is not significantly higher than that of *Abbott's* (1936) even if only her cases of bacterial endocarditis and bronchopneumonia are counted, and not including the ill-defined group of "cerebral causes of death" in which bacterial infections are not listed separately from other diseases.

Five cases of meningitis occurred in 66 cases of asplenia, including the above-mentioned case without cardiovascular malformations (A-25—167), but excluding two stillbirths (*Young*, 1947; *Author*, case 1) and two cases in which examination of the cranial contents was not permitted (*Boggs & Reed*, 2 cases, 1953). This incidence might seem to support the findings of *King & Shumacker* (1952). They emphasize that splenectomy performed before the age of six months may cause meningitis in a higher proportion than when it is carried out later. In the material presented here all cases of meningitis died at or before the age of 10 months. The similarity between this material and that presented by *King & Shumacker* may only be apparent, however, as both series are very small. As mentioned, the occurrence of infections in the present material is not significantly higher than in that of *Abbott*. Besides, another series of splenectomies carried out in infancy does not tend to support the findings of *King & Shumacker*. Thus, in the Boston Children's

Medical Center material of 18 instances of splenectomy on infants below the age of one year, only two developed meningitis (*Howell*, 1955). These two cases had been splenectomized because of congenital thrombocytopenic purpura.

Boesen & Vendel (1955 a) found four instances of meningitis in an autopsy series from Scandinavia comprising 1,137 cases of congenital heart disease in children under four years of age. None of these four cases was associated with asplenia. There were five cases of asplenia in that material, none of which was reported to have developed meningitis. Ninety per cent of these 1,137 cases died before the age of one year (*Boesen & Vendel*, 1955 b).

In view of the evidence presented, the findings of four cases of meningitis in the material of cardiovascular malformations presented by the author cannot be said to support the view of *King & Shumacker* (1952) that the spleen *per se* should be of particular value in combating infections during infancy. *Howell* (1955) mentions the possibility that the occurrence of meningitis after splenectomy might be due to the underlying error that was the reason for splenectomy, as, for example, congenital thrombocytopenic purpura.

PART III

Congenital Malformations of the Heart and Great Vessels Associated with Splenic Anomalies other than Agenesis

Occasionally, cardiac defects are encountered in cases with hypoplastic spleens, and also in cases with multiple spleens. The cardiac malformations of these cases have many features in common with those lacking spleens. These cases will not be treated extensively in this paper. This has been avoided for several reasons. First, there is considerable difficulty in defining the terms hypoplasia and multiple spleens. Hypoplasia of the spleen may result as a sequela of disease other than maldevelopment. Multiple spleens are often encountered in the form of splenunculi associated with a main spleen. Second, the purpose of this paper is to study cardiac defects, the basic lesions of which appeared at approximately the same time during organogenesis. The absence of the spleen is taken to indicate that this time coincided with the early formative phase of development of that organ. Including any other type of malformed spleen would invite several sources of error in that assumption. It might seem reasonable to assume that organogenesis of the spleen went astray somewhat later in cases of hypoplasia or duplication of the organ. Taking this for granted, however, would be fallacious.

To substantiate the above statements, four cases of cardiac defects with malformed spleens will be described, with short comments added.

An example of hypoplasia of the spleen associated with congenital heart disease

Case 15

T.P.C. (C.H. A-51—287). 6-day-old white male, born 2 weeks prematurely. Three hours after birth he became cyanotic. Apneic periods developed gradually. During one of these spells the patient expired.

Autopsy. *Peritoneal cavity.* The liver was symmetric, with the gall bladder in the midline. The stomach was dextroposited. The appendix was in the left iliac fossa. There was a common mesentery. The great omentum was absent. The spleen (Fig. 26) was found behind the stomach in the right

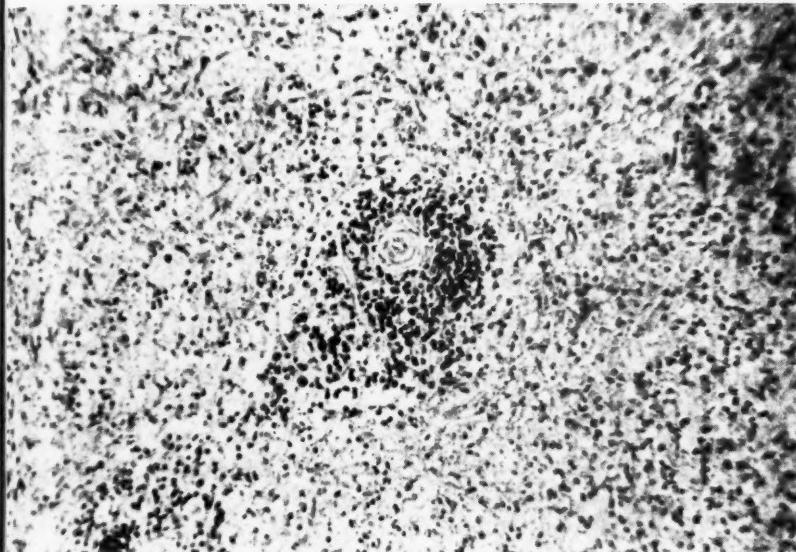


Fig. 26. Case 15. Section of hypoplastic spleen, with a small Malpighian follicle. $\times 136$.

hypochondrium and weighed 3 grams. The adrenals were fused in the midline. *Heart, lungs and great vessels.* There was levocardia. The right lung had three lobes, the left two. The inferior and superior venae cavae were connected with the right atrium. There was no left superior vena cava. There was completely anomalous pulmonary venous connection; a common pulmonary vein was connected with the innominate vein. This common pulmonary vein was interpreted as a partially persistent left superior vena cava. There was a 0.5 cm. interatrial septal defect without a valve in the area of the foramen ovale. There was an interventricular septal defect measuring 2×4.5 cms., the septum being reduced to a narrow wedge. There were four atrio-ventricular cusps, the anterior mitral being fused with the anterior tricuspid through the interventricular septal defect. The pulmonary orifice was atretic. The pulmonary trunk lay behind and to the left of the aorta. The aortic orifice had three well-formed leaflets and measured 4 cms. in circumference. There was a left aortic arch with normal branching. The ductus arteriosus was patent. The coronary artery pattern was unremarkable.

Anatomic diagnoses: Cor biatriatum triloculare; levocardia; 4-cuspid A—V valve; pulmonary atresia with transposition of the great arteries; patent

ductus arteriosus; anomalous pulmonary venous connection, complete common pulmonary vein (question of partially persistent superior vena cava) connected with the innominate vein; interatrial septal defect; symmetric liver; common mesentery; dextroposition of stomach; hypoplasia of spleen, with weight of 3 grams (normal equals 9 grams).

Comment. Case 15 displays anomalies of the cono-truncus that would qualify the case for placement in Type B: pulmonary atresia with transposition. There was an anomalous A-V valve with four cusps. The symmetric arrangement of the superior vena cavae, the liver and the mesentery is evident. The septal defects and the common pulmonary vein are further characteristics that are encountered in cases of agenesis of the spleen. In short, the anomalies are indistinguishable from those of splenic agenesis belonging to Type B, save for the hypoplasia of the spleen. That organ was examined histologically and consisted of splenic tissue (Fig. 26).

Two examples of double spleen associated with congenital heart disease

Case 16

L.C. (C.H. A-41-26). 10-day-old female, not reported to have been cyanotic at birth. At 2 days of age she began to vomit. An exploratory laparotomy was performed, and intestinal obstruction was found. After lysis of adhesions, the course went down-hill with evidence of persistent obstruction. Death occurred at 10 days of age.

Autopsy. Peritoneal cavity. Liver, symmetric. Stomach, transposed to the right. Two spleens anterior to the great curvature of the stomach measured $2.5 \times 1.4 \times 1.0$ and $1.6 \times 1.0 \times 0.7$ cms., respectively. The former had five distinct lobules and was situated superiorly to the latter. There was a diffuse peritonitis. *Heart, lungs, and great vessels.* There was levocardia. The right lung had two lobes and the left was incompletely divided into a third upper lobe. There was inversion of the sino-atrial region. All systemic veins were connected with the left atrium; there were bilateral superior vena cavae. The right connected with the coronary sinus that drained into the left atrium. The right pulmonary veins were connected with the right atrium, the left with the left atrium. The right atrium was about $1/4$ the size of the left. There was fenestration of the fossa ovalis, the valve leaflet of which was situated on the right side of the septum. The A-V valves were unremarkable. The aortic orifice equaled the pulmonary in diameter and there was no transposition of the great arteries. There was a left aortic arch with normal branching. The coronary pattern was not unusual. The azygos vein was on the left and drained into the left superior vena cava.

There was a hemiazygos vein that drained into the right superior vena cava. The azygos and hemiazygos veins were interpreted as being persistent post-cardinal veins. There was no innominate vein.

Anatomic diagnoses: Levocardia; inversion of sino-atrial region and its connections; anomalous pulmonary venous connections, partial; right pulmonary veins connected with the right atrium and left pulmonary veins with the left atrium; anomalous systemic venous connection, total, all systemic veins connected with the left atrium (RSVC by way of coronary sinus); azygos vein connected with left superior vena cava; hemiazygos vein connected with right superior vena cava; fenestration of fossa ovalis; symmetric liver; dextroposition of stomach; dextroposed double spleen; peritonitis, postoperative, (intestinal obstruction, neonatal, postoperative).

Comment. Case 16 had two dextroposed spleens, one of which was divided into five lobules. No anomalies were found in the cono-truncus region, nor of the atrio-ventricular valves. The anomalies were limited to the venous connections, with inversion of the sino-atrial region. This case is somewhat different from the cases without spleen. A persistent right superior vena cava connected with the coronary sinus draining into the left atrium is not encountered in any of those cases. It is interesting to note the normal cono-truncus and A—V regions.

Case 17

G.M. (C.H. A-51-173). $7\frac{1}{2}$ -month-old white male. Cyanosis developed shortly after birth. Cyanosis was more prominent on crying. Cyanosis gradually increased and daily attacks appeared. During one of these spells the patient expired at the age of $7\frac{1}{2}$ months.

Autopsy. Peritoneal cavity. The liver was symmetric and the gall bladder was in the midline. The stomach was on the left. There was a common mesentery. Two spleens were found to the left of the gastro-colic ligament. They measured $3.5 \times 1.5 \times 1.0$ and $1.7 \times 1.7 \times 1.5$ cms., respectively.

Heart, lungs and great vessels. Levocardia, lobation of lungs unremarkable. The inferior vena cava entered the right atrium, as did the right superior and the persistent left superior vena cava. The latter entered the atrium by way of the coronary sinus. The two pulmonary veins, one from each lung, joined to form a common pulmonary vein that was connected with the right superior vena cava. There was a patent foramen ovale opening into a left rudimentary atrium into which no vessels emptied. The mitral orifice was atretic. The interventricular septum was absent and no rudimentary left ventricle could be found. The right atrium entered the common

ventricle through a tricuspid valve measuring 3.5 cms. in circumference. The aorta arose anteriorly and to the right of the pulmonary trunk. The pulmonary orifice showed a valvular and an infundibular stenosis. The pulmonary valve had three leaflets. The pulmonary trunk measured 0.8 cm. in circumference, the orifice 0.5 cm. in circumference; i.e., there was a post-stenotic dilatation. No ductus was found. There was a right aortic arch with branching that was a mirror image of the normal. The coronary arteries were not unusual.

Anatomic diagnoses: Cor biventriculatum triloculare; levocardia; mitral atresia; transposition of the aorta with pulmonary stenoses, valvular and infundibular; anomalous pulmonary venous connection, total, with right superior vena cava; persistent left superior vena cava draining into coronary sinus; right aortic arch; symmetric liver; common mesentery; double spleen.

Comment. Case 17 had two spleens. There were mitral atresia and pulmonary stenosis with transposition of the great arteries. It would fit into Type B, like Case 15. The abnormal cono-truncus is associated with an anomalous A—V region.

An example of tripartite spleen associated with congenital heart disease

Case 18

M.A.P. (C.H. A-51-32). 4-month-old white female with cyanosis at birth. Gradually the patient went into respiratory distress, and cyanosis increased. She expired at the age of 4 months.

Autopsy. Peritoneal cavity. All the abdominal organs were normally situated. There were three spleens, measuring from 1 to 3 cms. in greatest diameters and weighing 18 grams together. They were found in the left upper quadrant behind the stomach. *Heart, lungs and great vessels.* Levocardia. Normal lobation of lungs. The systemic veins were connected with the right atrium, the pulmonary veins, with the left, as normally. The foramen ovale was patent and measured 0.2 cm. in diameter. The atrio-ventricular valves were unremarkable. There was a membranous interventricular septal defect measuring 0.5 cm. in diameter. The aorta was approximately 50 per cent dextroposed, overriding the interventricular septal defect. The aortic valves were not unusual. There was a right aortic arch. The pulmonary orifice was stenotic, and the leaflets were malformed and composed of small irregular thickenings of the endocardium at the circumference of the valvular ring. There was a post-stenotic dilatation of the pulmonary trunk, measuring 2.4 cms. in circumference just above the valvular ring. The right ventricle appeared normal.

Anatomic diagnoses: Levocardia; tetralogy of Fallot; dextroposition of aorta; pulmonic stenosis, valvular; right aortic arch; hypertrophy of right ventricle; patent foramen ovale; interventricular septal defect, membranous; three spleens.

Comment. Case 18 had three spleens, together weighing 18 grams (normal at this age, 16 grams). There were anomalies of the cono-truncus to qualify this case for placement in Type B, pulmonary stenosis with transposition. No A-V anomalies were found. This case is an example of abnormal cono-truncus without A-V anomalies.

As mentioned by *Putschar* (1934), cases with multiple spleens may occur with or without congenital heart disease. That author gives several examples from the literature showing that congenital heart malformation is not a constant feature of cases with multiple spleens. *Putschar* mentions 14 cases with double spleen two of which had associated heart malformations, and 16 cases with multiple spleens six of which were associated with congenital heart disease. *Putschar* briefly reviews several cases of multiple spleens where the heart is not mentioned.

To illustrate the occurrence of multiple spleens without cardiac malformation the following example is given.

An example of multiple spleens without associated congenital heart malformation

Case 19

S.McG. (C.H. A-43-197). A 1-year-old white female expired with signs of fulminating infection 12 hours after admission to an outside hospital.

Autopsy. Peritoneal cavity. The right lobe of the liver was greater than the left. The gall bladder was in the midline. The stomach was dextroposed and the great curvature reached the lateral abdominal wall in the right anterior axillary line. The pylorus was situated immediately below and slightly to the right of the gall bladder. Included in the posterior attachment of the stomach and against the posterior abdominal wall there was a series of small spleens. The lowest measured $0.5 \times 0.5 \times 0.5$ cm. Above this one there were two approximated spleens measuring respectively $2 \times 1.2 \times 1.5$ cms. and $2.2 \times 1.8 \times 1.6$ cms. Three more accessory spleens were found more anteriorly, measuring $0.6 \times 0.6 \times 0.6$ cm., $0.3 \times 0.2 \times 0.1$ cm., and $0.1 \times 0.1 \times 0.1$ cm. There was only one umbilical artery. The entire colon was intraperitoneal and there was a common mesentery. The cecum was in the left fossa ilica. *Heart and great vessels.* There was levocardia. The great veins were moderately distended but showed the normal anatomic features. The superior and inferior venae cavae and the coronary sinus

entered the right atrium; and the pulmonary veins, the left. The foramen ovale was probe-patent. There was no interventricular septal defect. The great arteries were normal. The valve and wall measurements of the heart were: A.V., 2.9; P.V., 3.2; M.V., 3.5; T.V., 4; L.V.M., 0.9 and R.V.M., 0.5 cms. The coronary arteries were normal.

Final diagnosis: Unexpected death; pneumococcus Type VI bacteremia; mal-rotation of gastro-intestinal tract; dextroposition of stomach and pancreas; multiple spleens.

Comment. This is a case where 6 spleens were found but no signs of congenital heart malformation. There was evidence of partial abdominal situs inversus with dextroposition of stomach and pancreas and a common mesentery, features that *Putschar* considers to be common in these cases.

Discussion

As can be seen from these case reports and the examples from the literature to follow, there are great similarities, except for Case 19, between these cases and those with absence of spleen; but the anatomic variation in the cases just presented is still wider than in cases with splenic agenesis. Because of their similarity, they have been mentioned in this part. Because of the proportionally wide anatomic variation and because congenital heart disease is not as constant a feature in these cases they will not be included in the material of absent spleens.

In the literature, several cases similar to those outlined in this part are found. Reference may be made to the following examples, chosen at random, and encountered in the literature during search for cases without spleens.

Lochte (1898) found two dextroposed spleens in a case of transposition of the great arteries with pulmonary stenosis and transposed A-V valves in levocardia. The tricuspid valve was irregular and malformed. There were anomalous systemic and pulmonary venous connections.

Geipel (1903, Case 1) describes a case of dextrocardia with transposition of the great arteries, single bicuspid A-V valve and six separate, equal-sized small spleens.

Royer & Wilson (1908) report a case with five dextroposed spleens, levocardia, transposition of the great arteries, malformed A-V valves, septal defects, and symmetric liver.

Miller (1925) describes a case with six small, dextroposed spleens. There were levocardia, transposition of the great arteries, fused A-V valves, septal defects, anomalous venous connections, and trilobed lungs.

A rudimentary spleen is described in the paper by *Doliopoulos & Maillet* (1952). It concerns a 4-year-old female who expired on the operating table during preparations for a shunt operation. Autopsy revealed pulmonary atresia with transposition of the great arteries, patent ductus arteriosus, single A-V valve and single ventricle. A "rudimentary spleen" was situated in the right hypochondrium ("la rate rudimentaire se trouve à droite"). No weight or size of the organ was recorded, nor was it stated to have been examined histologically. This case is noteworthy, considering the fact that, grossly, an accessory liver might easily be mistaken for a spleen. This mistake was made in gross examination of two of the present author's cases (Case 9, Type B; Case 11, Type C). Not until the alleged spleens in these cases were examined histologically was their true nature of accessory livers ascertained (Figs. 20 and 24). However, as Case 15 shows the similarity of the associated anomalies in a case of hypoplastic spleen to those with agenesis of the spleen, the rudimentary spleen of *Doliopoulos & Maillet* might well have been a hypoplastic spleen. The possibility of an accessory liver, nevertheless, seems equally likely.

An almost identical case to that of *Doliopoulos & Maillet* is reported by *Donzelot et al.* (1949). It concerns a 4-year-old female who died on the operating table during operation. The autopsy revealed levocardia, septal defects, pulmonary atresia, patent ductus arteriosus, single ventricle and single A-V valve. In this case, also, there was a transposed rudimentary spleen. It is not reported measured or weighed; nor is it stated to have been examined histologically. The same discussion applies here; the possibility of an accessory liver has not been ruled out.

These two cases are remarkable also because of the age of the patients. Only three cases in the whole material of agenesis of the spleen were 4 years of age or more (4-8 years, *Campbell et al.*, 1953; *Campbell & Forgacs*, 1953). Whether this speaks in favor of agenesis or hypoplasia of the spleen is open to debate.

Summary

Cases with hypoplastic or multiple spleens may show cardiac defects and anomalies of the great vessels indistinguishable from those with agenesis of the spleen.

Four examples of this fact are given in short case reports.

Six random examples from the literature confirm these statements.

The possibility of mistaking an accessory liver for a spleen, grossly, has been pointed out. Two cases in the literature where this reasoning may

apply have been found, and two of the author's own cases with accessory livers without spleens have been referred to.

The significance of hypoplastic or partitioned spleen is difficult to ascertain. The interpretation of the time during embryogenesis when this type of maldevelopment occurred is fallacious.

As the purpose of this study is to catch cardiac deformities that can be assumed to have gone astray at the time of early splenic organogenesis, it would be inviting too many sources of error to include cases with malformed spleens of the type outlined above, especially since congenital heart disease is not a constant feature.

PART IV

Discussion. Cono-Truncus Anomalies and Malformations of the A-V Region, and their Possible Relationship in Cases of Congenital Asplenia

Congenital heart malformations commonly occur as isolated manifestations of dysontogenesis (*Abbott, 1936; Taussig, 1947; Edwards, 1953 a; Rossi, 1954; Kjellberg et al., 1955*). However, syndromes do occur in which malformations of the heart and great vessels are associated with various anomalies in other organs. Syndromes with malformations of the extremities have been described: for example, the Ellis—van Creveld syndrome with ectodermal dysplasia, polydactyly, and chondrodysplasia associated with congenital heart disease, usually an interventricular septal defect (*Ellis & van Creveld, 1940*). Another is Marfan's syndrome, with a tendency to great height, arachnodactyly, looseness of joints, scoliosis, spina bifida, ocular abnormalities, and defects of the cardiac septa, in addition to medionecrosis of the aorta (e.g., *Hsi-Lin Tung & Liebow, 1952*). Moreover, multiple anomalies in association with cardiac defects are found in such a condition as mongolian idiocy (*Taussig, 1947; Rossi, 1954*). The syndromes mentioned, however, contain many variables, and not a constant easily defined single anomaly. *Levinson et al. (1955)* have recently shown, for example, that mongolism is a variable condition without any constant developmental characteristic. Therefore, utilization of the associated defects in the above-mentioned syndromes to time the cardiac defects would be fallacious.

In the present material, consideration has been paid only to cases with heart malformations occurring together with absence of the spleen. That malformations of the cono-truncus and atrio-ventricular region are common without this associated splenic abnormality is obvious. Absence of an organ in childhood is an easily defined congenital abnormality. It has been thought valuable to analyze cases of congenital heart malformations which are associated with an abnormality of another organ, this latter anomaly being a constant feature of all cases. It has to be pointed out, however, that what is implied concerning pathogenesis of the heart malformations in the discussion to follow appears to be relevant only in cases of congenital cardiac defects associated with absence of the spleen.

A. On the Significance of Congenital Asplenia

The common denominator in the material presented is the absence of the spleen. Only autopsy cases with absence of the spleen associated with congenital malformations of the heart and great vessels have been included. A few examples of other splenic anomalies with congenital malformations of the heart and great vessels have been mentioned.

Absence of the spleen is considered rare (*e.g.*, *Kaufmann*, 1955). Its unusually high degree of coexistence with congenital malformations of the heart and great vessels has been repeatedly stressed (*e.g.*, *Putschar*, 1934). This is also revealed in the present material. Eleven of the cases presented have been examined at post-mortem at the Boston Children's Hospital. Twelve cases of absence of the spleen were found by the pathology department of that hospital during the years 1920—1953. The twelfth case, (C.H. A-25—167), as has been mentioned in Part II, Section C (pp. 00) showed purulent meningitis, suppurative otitis, and bronchopneumonia, and no associated malformations of the heart or great vessels. During those 34 years, 7,032 post-mortem examinations were performed on children. From that material the author checked all cases of congenital heart disease for the presence of multiple spleens or asplenia. The occurrence of 11 cases of cardiac malformations among 12 cases of asplenia is in agreement with *Putschar's* finding of 20 with that condition among 23 cases of asplenia in infancy.

To test the hypothesis that congenital heart disease occurs independently of asplenia in the cases presented, a "fourfold" table has been constructed, as shown below.

TABLE 2.

		Spleen		
		absent	present	total
Heart	abnormal	11	341	352
	normal	1	6,679	6,680
	total	12	7,020	7,032

A chi-square test of independence gives a P-value of less than 1:1,000. This shows that the data support the assumption that the occurrence of asplenia and congenital heart disease is correlated.

In adults, however, the association of cardiac malformations and absence of the spleen is found only rarely. *Putschar* mentions 15 cases, including only one with anomalous connections of the great veins and situs inversus of the thoracic viscera (*Bujalsky*, 1829). In adults, as pointed out, for example, by *Boggs & Reed* (1953), it is difficult to ascertain whether absence of the spleen is a congenital malformation or whether the situation is the result of postnatal destruction. The fact that absence of the spleen is associated with malformations of the heart and great vessels more often in children than in adults appears to be due to the severity of the associated anomalies of the heart and vessels. These defects lead to death in infancy or early childhood.

One of the effects that might seem to be due to the absence of the spleen is the occurrence of infections, meningitis in particular. In the material presented four cases had meningitis, not including the above-mentioned case without cardiac anomalies (A-25—167). This might appear to be in accordance with the findings of *King & Shumacker* (1952) who point out the high incidence of meningitis in infants on whom splenectomy was performed before the age of six months. As the cases presented here have severe malformations of the cardiovascular system, it seems, however, dangerous to draw conclusions from this apparent similarity. It is noteworthy, however, that all cases with meningitis in this material died at or before the age of 10 months. This may mean that the function of the spleen in combating infections is more important in early life than later. This has been discussed in Section C of Part II. As presented, the material under consideration does not give any further clues to the explanation of these facts.

However, the *main significance of the asplenia* in this context concerns timing of the associated abnormalities of the heart. As the spleen has been shown to form during the period of critical modeling of the heart, it is assumed that the material collected comprises cases in which the morphogenesis of the heart was disturbed at about the same time during embryogenesis. The absence of the spleen serves as an indication of this period of embryonic development.

The following discussion is based on two assumptions:

1. The absence of the spleen is interpreted as an agenesis, a failure of the splenic primordia to form. It is, in other words, assumed that a spleen was never formed during embryogenesis. Theoretically, it would seem possible that splenic primordia had developed and atrophied later during morphogenesis. An agenesis is, however, still interpreted as being the result of events that went into play at time when the organ in question was about to be formed (*Stockard*, 1921; *Lehmann*, 1955; *Werthemann*, 1955).

2. The early formative stage of development of the spleen is accepted as being its sensitive phase in morphogenesis. This assumption is supported by the views of teratologists, as mentioned. It is only assumed, however, for it has not yet been shown experimentally that the spleen, specifically, can be abolished if it is exposed to teratologic agents during this period. The assumption is supported, however, by the principle that all organs are most sensitive to teratogenic action in their early period of development (*Zwilling*, 1955; *Wrete*, 1955).

The etiology and pathogenesis of splenic agenesis is unknown. Teratologically it may be due to anoxia, vitamin deficiency, x-ray damage, toxic action of viruses or the influence of placental abnormalities, or it may be genetically determined. Whatever the cause of splenic agenesis may be, it may be assumed to be nonspecific; and however it is induced, the result is dependent on the time of teratogenic action (*Stockard*, 1921).

Various teratogenic agents have different critical periods of action (*Lehmann*; *Werthemann*), and various organs have their specific critical periods of development (*Zwilling*). The early formative stage of development is still considered to be the critical phase of development (*Zwilling*). This concept includes the exogenous as well as the endogenous (genetic) teratogenic action (*Lehmann*; *Werthemann*). In the case of exogenous agents, the length of time of exposure seems to play an important role (*Zwilling*). Furthermore, *Stockard* considers that the essential mode of teratogenic action is a decrease in the developmental rate and that the resulting malformation is always due to this slow rate of development.

Thus, the absence of the spleen may be looked upon as a result of developmental arrest ("Hemmungsmmissbildung", *Putschar*, 1934).

B. On Splenic Anomalies other than Agenesis

In Part III a few examples have been given of heart malformations associated with rudimentary or multiple spleens. As these types of splenic malformations may occur without congenital heart disease, as Case 19 shows, the significance of the anomalous spleen is obscure. Nevertheless, some cases have been reported, and examples from the literature have been alluded to, because of the obvious similarity between these cases and those lacking spleens.

As has been shown in Part I on embryology the splenic primordia may have the character of multiple hillocks. *Broman* (1921) describes the first splenic primordia as a poorly outlined area of thickening of the dorsal

mesogastrium that occurs about the end of the first embryonal month. Late in the third embryonal month notching ("Incisuren") appears on the surface that later is smoothed out normally (*Broman*, 1921). In the cases mentioned with multiple spleens it may be assumed that the teratogenic action struck the spleen during the period while these notches existed, causing an arrest of fusion of the incisures. Although the fusion had failed to occur, the spleen continued to grow, and partitioned; or multiple spleens, made up of approximately the normal amount of splenic tissue, resulted.

The period of fusion of the primitive splenic hillocks is not exactly known, nor does the present material give any certain clues to it. It seems likely, for the reasons given, that developmental arrest took place later in these cases of multiple spleens than in those lacking spleens. Although the material is small, this is evident from the heart malformations as well. The teratologic succession of cono-truncus malformations from the primitive and early, to the less primitive and late anomalies under consideration, appears to the author to be the following:

- a) Truncus arteriosus, persistent,
- b) Pulmonary atresia,
- c) Pulmonary stenosis, and
- d) Transposition of the great arteries without stenosis.

In the present material of asplenia, cases of (b) and (c) are most numerous, with 41 cases, or 59 per cent of the whole material (69 cases) belonging to those categories. Cases of (b) and (c) are about equally common, comprising 22 and 19 cases, respectively. Of the seven reported and reviewed cases with multiple spleens, three had pulmonary stenosis (*Lochte*, 1898; *Royer & Wilson*, 1908; *Miller*, 1925), and one had no anomalies of the cono-truncus (*Author*, case 16). None showed atresia of the pulmonary orifice or persistent truncus arteriosus. It should be noted that the case of hypoplasia of the spleen (*Author*, case 15) and cases with "rudimentary spleens" all had atresia of the pulmonary orifice (*Donzelot et al.*, 1949; *Doliopoulos et al.*, 1952).

However small this material is, it may be inferred that cono-truncus anomalies are less "primitive" in cases with multiple spleens than in those with agenesis of the spleen. To the writer this seems to be evidence that the teratogenous action might have set in later in these cases. In other words, it confirms the method applied, using a malformed organ as an indicator of the approximate time of teratogenic action in "teratologic syndromes".

C. On the Pathogenesis of the Heart Malformations

Description of the *cono-truncus region* was accessible in 67 of the 69 cases, those of *Valleix* (1834) and *Bossert & Leichtentritt* (1920) being excluded. Sixty-five (97 per cent) of these 67 cases were reported to be abnormal, only the cases of *Birch-Hirschfeld* (1871) and *McLean & Craig* (1922) being described as normal in that region.

The *atrio-ventricular region* was adequately described in 58 of the 69 cases excluding the 11 cases of *Martin* (1826), *Valleix* (1834), *Kundrat* (2 cases, 1887 and 1888), *Garvin* (1927), *Bossert & Leichtentritt* (1920), *Jaccard* (1951), *Gasser & Willi* (case 2, 1952), *Boggs & Reed* (2 cases, 1953), and *Bush & Ainger* (1955). The cases of *Jaccard* and *Gasser & Willi* (case 2) were examples of *cor biloculare* and can be assumed to have contained common atrio-ventricular ostia although no descriptions of the atrio-ventricular valves have been included in the reports. The cases of *Boggs & Reed* were examples of hearts with large interatrial and interventricular septal defects (question of *cor biloculare*); no adequate description of the atrio-ventricular valves is included in the report. In Case 1 there was pulmonary atresia. Despite this fact, the authors state, "except for the right-sided position of the aortic valve, the remaining valves were not unusual". In their Case 2 they state, "the aortic, mitral and tricuspid valves were not remarkable except in position". In *Bush & Ainger's* case the tricuspid valve is described and stated to be situated to the left, while the right-sided atrio-ventricular valve is not described at all. Of the mentioned 58 cases with adequate descriptions of the atrio-ventricular valves, 56 (97 per cent) showed abnormal atrio-ventricular ostia, as accounted for in Section C of Part II (pp. 60), the two cases of *Birch-Hirschfeld* and *McLean & Craig* being described as normal. If the cases of *Jaccard*; *Gasser & Willi* (case 2); *Boggs & Reed* (2 cases); and *Bush & Ainger* are included, the percentage would be the same (61 of 63 cases).

All cases with abnormal atrio-ventricular regions had malformations of the *cono-truncus*. All cases with malformations of the *cono-truncus* and adequate descriptions of the atrio-ventricular region showed the latter to be anomalous. Two cases, (*Birch-Hirschfeld*, 1871; *McLean & Craig*, 1922), with adequate descriptions of both regions showed them to have normal *cono-truncus* and *A-V* regions.

1. Isolated occurrence of *cono-truncus* and *A-V* anomalies

The pathogenesis of *cono-truncus anomalies* has been studied extensively since the time when *Rokitansky* (1875) proposed a theory explaining transpo-

sition of the great arteries, stenosis of the arterial ostia and septal defects on the basis of a primary deviation of the septation process. This theory, later extended by *Geipel* (1899 and 1903) and *Mönckeberg* (1924), was opposed by *Spitzer* (e.g., 1923; *Spitzer, Lev & Vass*, 1951) who claimed to be able to explain all malformations of the heart on the basis of his phylogenetic theory. *Spitzer*, regarding transposition, emphasized detorsion of the conus as the cause of obliteration of the normal (left) human aorta that was replaced by a persistent reptilian (right) aorta evanescent in the human embryo. This concept was strongly opposed by *Pernkopf & Wirtinger* (1933 and 1935) who, on the basis of ontogeny, regarded inversion of the conus with growth of an abnormal septum as the essential cause of transposition. Excellent discussions of the above theories will be found in papers by, for example, *Harris & Farber* (1939), *Bredt* (1935/36 and 1936) and *Doerr* (1938, 1943, and 1955 a).

Isolated malformations of the *atrio-ventricular region* are more rare than those of the *cono-truncus*. Anomalies of the A—V region are not as easily detected at post-mortem examination as are *cono-truncus* anomalies. The latter are usually obvious as soon as the pericardial cavity is opened. The anatomic variation in malformations of the *cono-truncus* is greater than in those of the *atrio-ventricular region*. For these reasons, the literature on malformations of the *atrio-ventricular region* is comparatively scarce. Among classical studies, those of *Sato* (1914) and *Mönckeberg* (1915 and 1924) may be mentioned.

Recently there has been great interest in the surgical correction of interatrial septal defects and anomalous venous connections (*Gross*, 1953; *Kirklin*, 1953; *Geraci & Kirklin*, 1953). The clinical diagnosis of interatrial septal defects and anomalous venous connection is becoming more accurate by the addition of new techniques (e.g., *Varnauskas & Werkö*, 1954; *Kjellberg, Mannheimer, Rudhe & Jonsson*, 1955). Possibly for these reasons, there is an increasing interest in anomalies of the "venous end of the heart". This is reflected by a gradually expanding literature on this subject. Among American pathologists who have published several papers on the malformations of this region of the heart is *Edwards* (*Rogers & Edwards*, 1948; *Edwards & Burchell*, 1949; *Edwards & DuShane*, 1950; *Edwards*, 1953 b; *Becu, Tauxe, DuShane & Edwards*, 1955). Also, German pathologists have recently made important contributions to the pathology of this region (*Doerr*, 1952 a and b; *Kiss, Partilla & Pernkopf*, 1954). *Doerr* (1955 a), mentions that his coworker, *Kl. Goerttler*, is occupied with a study on the transposition of the veins. Embryologists also have recently contributed important studies on this region, as evidenced by *Shaner's* papers (1949 and 1951).

2. *Malformations of the cono-truncus and the A—V region in asplenia as a pathologic complex*

The isolated occurrence of cono-truncus anomalies and malformations of the atrio-ventricular region has thus been thoroughly investigated, as is evident from the references quoted above. However, anomalies of one of these regions, associated with malformations of the other, have aroused comparatively little interest. The studies performed have been limited largely to cases of mitral or tricuspid atresia. These malformations of the atrio-ventricular region are always, in tricuspid atresia, and often, in mitral atresia, associated with anomalous cono-truncus regions (*Edwards*, 1953 a). Mitral atresia is often combined with aortic atresia. Tricuspid atresia is always associated with some anomaly of the cono-truncus, as, for example, pulmonary stenosis (atresia) or transposition of the great arteries.

The possible *linkage* of malformations of the two regions has been mentioned in tricuspid atresia (*Bredt*, 1935/36; *Lev*, 1953 b). *Spitzer* (1951) pictured an influence of the cono-truncus anomalies upon the atrio-ventricular region, causing for example, transposition of the A—V ostia.

Shaner's (1949 and 1951) valuable embryologic approach led to the theory that anomalous atrio-ventricular canal cushions might cause malformations of the cono-truncus region of the heart. While dissecting 15,000 pig embryos, *Shaner* (1949) encountered 35 with abnormal hearts. Fifty per cent of these showed anomalous A—V canal cushions. *Shaner* considers that the anomalous A—V canal cushions of these hearts prevented the normal migration of the aorta into the left ventricle. He considers this migration essential to the normal evolution and septation of the cono-truncus, and arrest of it would result in malformations of that structure.

This concept corresponds well with the hypothesis of *Doerr* (1938) that the shape of the entire cono-truncus is decisive in its normal or abnormal septation. Supported by *Shaner's* observations on pig embryo hearts, *Doerr* (1952 a and b; and 1955 a) further elaborates this concept. *Doerr* (1952 b) considers the incidence of A—V anomalies associated with congenital pulmonary and aortic stenosis, 30 and 50 per cent, respectively, as evidence that A—V anomalies are primary to those of the cono-truncus in *certain* cases of heart malformations, mentioning congenital stenosis of the aortic and pulmonary ostia as examples.

As pointed out by *Bredt* (1935/36 and 1936) a *linkage* between anomalies of different portions of the heart ("gekoppelte Missbildungen") may, theoretically, be divided into two main groups,

- I. Dependent (conditional) linkage,
 - a) equivalent and mutually independent (due to the same cause),
 - b) reciprocally dependent (cause-effect relationship),
- II. Absolute (unconditional) linkage,
 - a) equivalent and mutually independent (due to the same cause),
 - b) reciprocally dependent (cause-effect relationship).

Group I concerns an association of anomalies that is not constant, but may occur under given circumstances. Group II comprises anomalies that are always associated, so that if a certain anomaly occurs the other must be present.

In an extensive discussion on the subject of linkage, *Bredt* (1935/36) considers that most of the linked anomalies, as, for instance, tricuspid atresia, are examples of Group I (a). It should be pointed out that his discussion is concerned only with linkage between *anomalies per se*. If, however, a *linkage between malformed regions* is accepted instead of between specific malformations, such a condition as tricuspid atresia would be an example of Group II. This reasoning is valid, as tricuspid atresia is always associated with malformations of the cono-truncus, as mentioned previously. The associated malformations of the cono-truncus are either stenosis (atresia) or transposition. Whether the associated anomalies in tricuspid atresia are linked in an (a) or a (b) fashion is not clear. It remains to be evaluated whether tricuspid atresia and the associated cono-truncus anomaly are due to the same cause, or whether there is a cause-effect relationship.

The discussion on the pathogenesis of tricuspid atresia (*Bredt*, 1935/36; *Edwards*, 1953 a) is impaired by lack of evidence of the time during morphogenesis when development of the heart was disturbed. Assisted by facts like the presence of valvular tissue in an atretic pulmonary orifice, or the presence of an interventricular septal defect, timing of the tricuspid atresia has been attempted (see *Edwards*, 1953 a). The time during embryogenesis when the atresia of the tricuspid orifice occurred is likewise unknown. There is no unanimity of opinion about whether atresia occurred before or after partitioning of the atrio-ventricular canal (*Bredt*, 1935/36; *Edwards*, 1953 a).

Equally obscure is the coexistence of mitral and aortic atresia that may occur (*Edwards*, 1953 a). This coexistence would be an example of Group I in the above outline, as mitral and aortic atresia may occur separately. *Edwards* (p. 406 b, 1953 a) points out that "for some occult reason there seems to be a secondary fusion of the developing [aortic] cusps". In these cases, *Edwards* seems inclined to accept fetal inflammation (*Farber & Hubbard*, 1933) as the most likely cause of the atretic aortic orifice.

In this context it may be interesting to note that the present material contains five cases of mitral atresia but not a single instance of aortic atresia. Examples of pulmonary atresia are, however, numerous (22 cases). The absence of aortic atresia cases would perhaps indirectly tend to support the hypothesis of *Farber & Hubbard* (1933) of this malformation's being the result of fetal inflammation, if, in the present material, developmental arrest not due to fetal inflammation should be accepted as the cause of the cardiac malformations present.

As pointed out above, the usual difficulty in understanding the developmental basis for any given malformed heart is the lack of knowledge of the time when the development of the heart went astray. In the present material there is a common denominator outside the heart that may be taken as an indicator of that time, the absence of the spleen.

It was shown by the author in Part I that early splenic primordia exist while the cono-truncus and the atrio-ventricular region are being partitioned. There is evidence that the fusion of the atrio-ventricular canal cushions occurs before the septation of the cono-truncus is completed. The final differentiation of the A-V canal cushions into valves, however, is accomplished after the complete separation of the cono-truncus.

The early formation of the spleen is accepted, teratologically, as its most sensitive stage of development (Assumption 2). The malformed hearts in the present material show anomalies of structures that appear to be in a critical phase of modeling during early splenic organogenesis. It follows that the teratogenic action on the heart and spleen took place simultaneously.

Agenesis of the spleen is accepted as the result of developmental arrest ("Hemmungsmisbildung", *Putschar*, 1934). It seems logical to look upon the malformations of the heart and great vessels presented here as examples of arrested development. Most authors agree that congenital malformations of the heart are usually due to developmental arrest (e.g., *Bredt*, 1936; *Doern*, 1955 a).

That organogenesis has been interrupted in the cases under consideration is further supported by the following evidence. The septation of the heart has been interrupted, as shown by the presence of 32 cases of *cor bilobatum*. Further proof of septation arrest is furnished by the occurrence of 18 cases with defects in the area of the *ostium primum*, the *cor bilobatum* cases not included. Interruption during embryogenesis of the normal resorption of the common pulmonary vein (*Buell*, 1922; *Auer*, 1948) occurred in 20 cases. In 36 cases the development of the pulmonary venous channels stopped at various levels, thus establishing connections with various systemic channels, including the right atrium, and resulting in anomalous pulmonary venous

connections. Systemic veins also display interrupted development, showing anomalous connections in 31 cases, including only those in close proximity to the heart.

Thus it has been shown that:

1. The heart malformations under consideration may be looked upon as being the result of developmental arrest;
2. the absence of the spleen in these cases is looked upon as the result of arrested development occurring in early splenic formation;
3. as the spleen is absent in all cases, it may be assumed that the organogenesis of the heart in all cases was disturbed at approximately the same time;
4. the malformed hearts display a high proportion of atrio-ventricular anomalies of various types (97 per cent);
5. there is also a high incidence of cono-truncus anomalies (97 per cent);
6. all cases showing atrio-ventricular anomalies have malformations of the cono-truncus;
7. all cases with malformations of the cono-truncus and adequate description of the atrio-ventricular region have malformations of the latter; and finally,
8. that the two cases with *normal* cono-truncus regions also had *normal* atrio-ventricular regions.

So far, the following *general conclusion* is achieved: in cases of congenital heart malformations displaying absence of the spleen, there appears to be a linkage between the atrio-ventricular and cono-truncus regions of the heart, malformations of one region always being associated with malformations of the other. This general conclusion is valid only under the condition stated, that is, only when the spleen is absent.

In order to investigate a possible presence of a linkage between the cono-truncus and the atrio-ventricular region in asplenia, a chi-square test on the independence of these two regions has been carried out, giving a P-value of less than 1:1,000. The data therefore support the assumption of the linkage mentioned.

If there is an absolute linkage between the two regions of the heart in cases of agenesis of the spleen, two theoretically different mechanism may have been in operation to produce the anomalous regions. In the theoretical classification of linkage, there are two subgroups of each of the two main groups. The question of whether there may be a cause-effect relationship between the malformations of the cono-truncus and atrio-ventricular region, or whether the malformations of the two regions are due to the same cause must be discussed.

3. Question of whether malformations of the cono-truncus and A—V region in asplenia are due to the same cause

A simultaneous and independent teratogenic action on the two regions of the heart must be considered, particularly as the anatomic variation of the anomalies is so wide. There is no constant occurrence of one type of cono-truncus malformation always being associated with one type of atrio-ventricular anomaly. In the present material the cono-truncus displays three types of malformations: persistent truncus arteriosus, pulmonary stenosis (atresia), and transposition of the great arteries. The atrio-ventricular region also exhibits a variety of malformations. In the material presented, the variation in the pathology of that region is even greater than in that of the cono-truncus. There are a common A—V ostium with varying numbers of cusps, mitral atresia, tricuspid atresia, and double bicuspid A—V valves. As far as the specific malformations are concerned, there is no constant linkage.

Apart from the wide anatomic variations of anomalies in these regions, there is another reason to consider an independent teratogenic action on the cono-truncus and atrio-ventricular region. They have one tissue component in common, the gelatinous reticulum. This substance is vital for the division of the A—V canal and the septation of the cono-truncus. Hypothetically, an arrest of the growth rate of this substance would seriously interfere with the normal evolution of these structures.

There are different mechanisms that might produce inhibition of growth in general, and probably of the growth of the gelatinous reticulum as well. *Oxygen deficiency* may cause cardiovascular anomalies as has been shown experimentally (*e.g.*, Schellong, 1955). After prolonged oxygen deficiency the concentration of ribonucleic acid is lowered in embryonal tissue, as shown experimentally (Leder, 1955). Ribonucleic acid decreases gradually during embryonic life as protein synthesis is diminishing (Caspersson & Thorell, 1941). It follows, theoretically, that hypoxia of the gelatinous reticulum would lower the growth rate of the substance and thus interfere with septation.

There is a high incidence of cono-truncus anomalies in the offspring of pregnant rats after being fed a diet deficient in pteroylglutamic acid (Baird *et al.*, 1954). *Antifolic acid* is known to be a growth inhibitor and it may have acted on the gelatinous reticulum, causing abnormal septation. In their paper, Baird *et al.* preliminarily reported the cono-truncus anomalies, and stated that histologic studies of the early phases of cardiac development were in progress. These authors did not report any associated defects of the

atrio-ventricular region. Possible defects in the latter region would not be clearly revealed on gross examination of newborn rats.

Another mechanism resulting in mutually independent defects of the cono-truncus and atrio-ventricular region is proposed by *Farber & Hubbard* (1933). They suggested that *fetal endomyocarditis* might be accepted as a causative factor in producing stenosis (atresia) of the cardiac ostia without the resulting anomalies necessarily being linked in a cause-effect sense. In the present material, however, the evidence points in the direction of developmental arrest, as shown by the association of numerous malformations of other organs. In the cases concerned there is no evidence of end results of inflammatory processes in the conventional sense. However, theoretically, inflammation may be accepted in general as a possible cause of developmental arrest, although this reasoning does not seem to apply here.

Thus, there is experimental evidence that may point in the direction of malformations of the cono-truncus and the atrio-ventricular canal being due to the same cause, a possible defect in the gelatinous reticulum.

In the experimental work on animals so far published, no report has been given on the association of cardiac anomalies and absence of the spleen. This may not be relevant in one way or another, as the consequences of such an association depends on the formation of the spleen and cardiogenesis being synchronous. This synchronism has been shown by the writer to exist in man. The animal still has to be found in which the spleen is formed during the same phase of cardiogenesis. To gain experimental support for the association of atrio-ventricular anomalies with splenic agenesis it is important to know at what period in cardiogenesis the spleen appears in the animal in question. On this point, therefore, further investigations are necessary.

In summary, an unknown teratogenic agent might have acted on the cono-truncus and atrio-ventricular region independently. Thus, this mechanism cannot be ruled out as an explanation of the pathogenesis of the associated cardiac malformations.

4. Question of whether there is a reciprocal dependence between the cono-truncus and the A-V region in cases of asplenia with congenital cardiac malformations

Even if it cannot be ruled out that the abnormal atrio-ventricular and cono-truncus regions are the result of the same teratogenic action and that they are independent of each other, there are facts in the present material that tend to contradict this view. First, there is a high incidence of cono-truncus anomalies, 97 per cent. Second, atrio-ventricular malformations occur

in 97 per cent of the cases (a slightly smaller group, due to inadequate description of this region). Third, the atrio-ventricular anomalies are always associated with malformations of the cono-truncus in this material. Fourth, all cases with anomalies of the cono-truncus have malformations of the atrio-ventricular region, if only cases with adequate description are considered. Although the material is small, comprising only 69 cases, these circumstances are very unusual.

Doerr (1952 b) found in cases of congenital pulmonary and aortic stenosis that the atrio-ventricular region was anomalous in 30 per cent of the first and 50 per cent of the second. In transposition of the great arteries, *Doerr* found abnormal A—V regions in 33 per cent. In malformed pig embryo hearts, *Shaner* (1949) encountered anomalous atrio-ventricular canal cushions in 50 per cent of cases with cono-truncus malformations. These figures may appear low in comparison with the incidence in the present material. The reason for this apparent discrepancy seems to lie in the method of selection of the material presented here. The high incidence of A—V anomalies in this material seems to be indirect evidence that this region was disturbed synchronously with the spleen.

The question of whether one region may be primary in causing defects of the other in cases of asplenia seems difficult to answer. There is coexistence of malformations of the two regions in all cases, and if one region is normal the other is also normal. However, in the light of recent observations, a discussion of some of the possible mechanisms in producing the linkage described in the material presented may not be entirely barren.

In the section on embryology (Part I) reference has already been made to *Doerr's* concept of the conflict zone between the cono-truncus and the atrio-ventricular canal. The atrio-ventricular aspect of this Achilles heel of the developing heart is considered by *Doerr* to be the essential target of teratogenic action in certain heart malformations. Obviously, this is in harmony with the findings of *Shaner*. According to *Shaner* and *Doerr*, malformations of the cono-truncus in certain cases will be understood if consideration is paid to malformations of the atrio-ventricular canal cushions. *Doerr* points out that the level of the future aortic and pulmonary valves is the same as that of the atrio-ventricular canal immediately before division of the latter and septation of the former. *Shaner* and *Doerr* picture the possibility of malformed canal cushions being an obstacle for the proper torsion (*Doerr*) of the cono-truncus and its migration (*Shaner*) into the left ventricle.

The vectorial torsion of the conus in the sense of *Doerr* seems to be a prerequisite for normal septation, a fact that is supported by the perfusion

experiments on glass models of embryonic hearts performed, for example, by *Bremer* (1931) and *Kl. Goerttler* (1955). Thus, septation of the cono-truncus may be looked upon as the result of the spiraling currents of blood rather than as a cause of the blood circulation. This is well shown by *Bremer* (1931) in the living chick embryo heart before septation has occurred, and by *Kl. Goerttler* (1955) on glass models of human embryonic hearts before septation.

As the spiraling currents have been shown to appear before septation is achieved they may be assumed to play an important causative role in partitioning. If the proper migration and torsion of the cono-truncus is interfered with, normal spiraling would be upset and would then cause abnormal septation because the zones of lessened lateral pressure ("seitendruckfreie Zonen" of *Kl. Goerttler*) would change.

One possible mechanism that would interfere with the proper migration and torsion of the cono-truncus is developmental arrest of the atrio-ventricular partitioning. Teleologically, the atrio-ventricular region would not be able to receive the migrating truncus between its right and left components if the fusion of the canal cushions did not occur at the proper time. As septation of the cono-truncus is well under way at the time of fusion of the canal cushions, it might proceed, but presumably in an abnormal fashion, causing various anomalies of the cono-truncus.

Four examples from the literature may be said to illustrate this possible arrest of migration resulting in cono-truncus anomalies. *Bredt* (1935/36) describes two cases in which the auricular appendages were found to the left of the arterial trunks. He refers to two further cases from the literature (*Dinner*, 1914; *Kettler*, 1932). In these four cases the arterial trunks were situated unusually far to the right. There was tricuspid atresia or stenosis in all cases.¹

In the present material there is a variety of atrio-ventricular anomalies. The most frequent of these is a common atrio-ventricular ostium. This occurred in 46 of 58 cases with adequate descriptions (79 per cent). In these instances, in other words, normal fusion of the A-V canal cushions had not occurred. It is conceivable that this failure of fusion might have been able to arrest the proper migration and vectorial torsion of the cono-truncus in the sense of *Shaner* and *Doerr*. These events are considered to be prerequisites for the blood currents to spiral around each other in such a way as to cause normal septation (the slack-water theory of *Bremer*, 1931; *Patten, Kramer & Barry*, 1948). If the slack-water theory for the septation of the cono-truncus is accepted, it seems conceivable that, theoretically, an undivided atrio-ventricular canal might upset the shape and localization of the cono-

See addendum on p. 110.

truncus so as to cause abnormal spiraling of the blood currents and abnormal septation of the cono-truncus. If, for example, the truncus arteriosus is straightened out, during its migration, by influence from the abnormal atrio-ventricular cushions the prerequisite for spiraling would be abolished; and the circumstances required for a persistent truncus arteriosus would result.

This admittedly grossly mechanical approach is not so easy to apply to the remaining atrio-ventricular anomalies present. In cases of *mitral* or *tricuspid atresia*, for example, it seems difficult to lay the responsibility for the associated cono-truncus malformations on the atrio-ventricular anomaly. *Lev* (1953 b) is, however, inclined to explain the pathogenesis of the various complexes associated with tricuspid atresia as being directly due to the latter anomaly. *Lev* seems to arrive at this conclusion mostly on hemodynamic grounds. From the morphologic point of view, a delayed fusion of the A-V canal cushions has to be considered as a possibility. From Part I it may be recalled that the division of the A-V canal is very close in time to the complete division of the cono-truncus. Morphologically, it is possible that a delayed fusion of the A-V canal cushions did occur, interfering with cono-truncus migration. Later, then, there was abnormal division resulting in atresia of one A-V ostium. Functionally, it must be recalled that the blood streams always have to pass the atrio-ventricular canal before they reach the cono-truncus. Thus, any modification of the blood streams occurring at the A-V ostium might be perpetuated in the cono-truncus. Considerations of the functional aspects of these events must be entirely speculative, but will be briefly considered in a later section.

If a cause-effect relationship between the malformations of the cono-truncus and the atrio-ventricular canal is accepted, the question arises as to whether the cono-truncus anomalies might be primary to those of the A-V region. *Spitzer* (1951), for example considered anomalous A-V ostia associated with cono-truncus malformations to be secondary to the latter. He specifically mentions transposition of the A-V ostia in this respect. *Spitzer* appears to accept this as the mechanism whenever malformations of the two regions are associated. Differentiation of the heart proceeds in a cephalo-caudad direction, that is from the cono-truncus to the sino-atrial end (*Patten*, 1949; *Copenhaver*, 1955). In accordance with the teratologic views quoted earlier, the early formative stage being considered more sensitive, the cono-truncus would be in its critical stage of development earlier than the atrio-ventricular canal. Although it is true in general that morphologic differentiation proceeds in a cephalo-caudad direction, there appears to be division of the atrio-ventricular canal by fusion of its cushions before septation of the cono-truncus is completed. In the phase of division of the A-V canal it might be

more sensitive towards teratologic action than the cono-truncus. In addition, there are normally two blood streams separated by gelatinous reticulum in the area of the atrio-ventricular canal before this happens in the cono-truncus region. Moreover, the two blood streams might be changed by an abnormal A—V region so as to upset the normal blood currents of the cono-truncus. This will be briefly discussed in a later section.

Early splenic formation has been shown to occur during fusion of the A—V canal cushions and before the septation of the cono-truncus is completed. The spleen is absent in all 69 cases presented here. There is a large number, 46 cases, in which fusion had failed to occur. In 12 other instances there were other A—V anomalies. In 97 per cent of the cases with adequate description of the A—V region there were A—V anomalies. To the writer this is evidence in favor of the view that these anomalies might have been primary to those of the cono-truncus in cases of agenesis of the spleen.

5. A short comment on the phylogeny of heart and spleen

The present material shows interesting analogies from the phylogenetic point of view. Thus, the spleen is absent in the lung-fish (*Dipnoë*) according to anatomists (e.g., Müller, 1916). The lung-fish shows phylogenetically the first evidence of a primitive interatrial septum, although it is functionally still a *cor biloculare*. In the next step in phylogeny, in the amphibia, the interatrial septum is "complete", and the spleen appears for the first time in phylogeny as a separate organ. These factors would invite speculations in the direction of Spitzer's phylogenetic theory of heart malformations. In the opinion of the writer, however, these facts only emphasize the pitfalls in analogies. It is always easy to find similarities between simple objects; and the reported malformations of the heart and great vessels tend to be simple rather than complex from the embryologic point of view.

6. On the possible relationship between morphology and physiology of the developing heart

In the preceding sections attention has been paid to morphology and the interrelationship of topographic structures in trying to explain the possible events that may lead to malformations of the cono-truncus in linkage with the atrio-ventricular region. Functional considerations, however, may add some important view-points to the understanding of the conditions under which the embryonic heart develops, and may cast some light on possible mechanisms that might have produced the malformed hearts described.

The first heartbeat in chick embryos occurs at about the 9—10 somite stage

(*Sabin, 1920; Patten, 1933 and 1949*), at which time the embryo chick heart is practically all ventricle and almost a straight tube. The contraction observed occurs in the right aspect of the common ventricle and proceeds in a caudo-cephalad direction. This is confirmed by electrocardiographic studies by *Hoff et al. (1939)*.

During this period of development and up to the time of the formation of proper atrio-ventricular and semilunar valves the valvular function of the heart is handled by the cardiac jelly of *Davis (1924 and 1927)*, by its being heaped up into mounds (*Patten, Kramer & Barry, 1948*). These authors have shown that the valvular pads consisting of cardiac jelly mounds are formed at the level of the future semilunar valves and at the site of the future atrio-ventricular valves. These mounds act in a reciprocal fashion, the closure at the atrio-ventricular level occurring "just after the sweep of contraction through the atrium has fully charged the ventricle with blood, and remaining closed while blood is being forced out through the conus". The contraction wave reaches the conal pads at the end of ventricular systole, thereby checking regurgitation. At this time the atrio-ventricular pads of cardiac jelly are open to permit filling of the ventricle for the next cycle.

Patten (1949) points out three important factors in the efficient propulsion of blood by the tubular heart:

1. The shifting of the pacemaker's location at different ages of the embryo, with its being constantly situated at the intake end of the heart, this being the start of propulsion.
2. The development of the above-mentioned valvular pads of cardiac jelly before the morphologic differentiation of valves proper, these minimizing the regurgitation and adding efficiency to the propelling force, and
3. adequate stroke volume (*Barry, 1948*).

This third factor, that might be called *Barry's law of the embryonic heart*, as equivalent to *Starling's law of the adult heart*, is actually the functional evaluation of the morphologic cardiac jelly of *Davis*. *Barry* points out that the systolic diameter of the tubular heart must be practically zero to keep up a cardiac output sufficient for the needs of the embryo. Further, the filling of the ventricle as well as its output depends on the diastolic diameter of the myocardial sleeve. Neither adult nor embryonic myocardium can shorten, in systole, more than a definite proportion of the diastolic length. If the stroke volume is going to be maintained, it follows that the embryonic myocardial diameter must be considerable. The thick layer of cardiac jelly, at least 45 per cent of the radius of the lumen in diastole, will transmit the

force of contraction radially against the small lumen. The circumference of the contracted myocardium is relatively large while the lumen is practically closed as its radius is increased by the thick layer of cardiac jelly. Thus, the cardiac jelly will increase the diastolic diameter of the myocardium enough for an adequate stroke volume.

Considering these facts in pondering the pathogenesis of the heart malformations in the present material, it would seem possible that any change of the cardiac jelly (gelatinous reticulum) at the region of future valves would seriously interfere with the physiology of the heart in the embryo. If the cardiac jelly should degenerate at the atrio-ventricular valves, this would result in regurgitation during systole, a process that would probably not improve the morphogenesis of the heart. In the cases with a common atrio-ventricular ostium, fusion of the canal cushions had failed. Presumably, this means that damage to the cardiac jelly had occurred here.

Any process that interferes with the proper function of the cardiac jelly would probably interfere with embryonal heart function. An arrested division or an abnormal fusion resulting in a common A-V ostium or an atretic A-V ostium may alter the physiology of the heart in the embryo in such a way as to cause malformations of other regions. The malformations would be linked in a physiologic sense.

These speculations by the author are based on experimental work on normal chick embryos (Bremer, 1931; Patten, Kramer & Barry, 1948). Mapping out the physiology of the abnormal embryo heart seems necessary to evaluate the role of altered hemodynamics as a cause of congenital cardiac malformations.

7. Practical and clinical considerations

It has been shown that in cases of congenital asplenia associated with congenital malformations of the heart and great vessels there is a high incidence of cono-truncus and A-V anomalies. The view of the writer is, that, in asplenia, the A-V anomalies may be primary to those of the cono-truncus. Whether or not this is accepted, it seems important to stress the frequent occurrence of the latter. The present study has been confined to cases lacking spleens, and it is possible that the close correlation between anomalous cono-truncus and A-V regions exists only in those cases. However, for the understanding of cono-truncus anomalies in general it seems important, in view of the evidence presented, that the A-V regions of all such cases should be studied with meticulous care at autopsy.

Furthermore, the material presented contains a large number of cases

with anomalous venous connections. It should be stressed that the mapping of these is possible only when dissection *in situ* is carried out. After the vessels have been severed, it is often impossible to trace their course and their connections. In the new cases presented here this *in situ* dissection has been the procedure.

A few clinical features of the cases of asplenia will be mentioned. This syndrome occurs most commonly in males. Of the 63 cases of this report in which the sex was stated, 40 were males and 23, females. Various races are represented: among them are two Negroes (*Shapiro*, 1930; *Leikin*, 1951); one is Chinese (*Hu*, 1929); and one is Japanese (*Kimura*, 1930). In 65 cases the age at the time of death was stated. Most of the cases, 55, fall within the age range of birth to 12 months. The stillbirths have not been included.

In four cases in which the clinical diagnosis of Tetralogy of Fallot was made operations were planned or performed (*Boggs & Reed*, case 2, 1953; *Polhemus & Schafer*, cases 2 and 3, 1952; *Campbell et al.*, case 3, 1953). Shunt operations in these cases were either followed by death shortly afterwards, or they failed because of hypoplasia of the pulmonary arteries or atresia of the pulmonary trunk, making an anastomosis impossible. It would seem necessary to rule out the Type B syndrome of asplenia in clinical cases of Tetralogy of Fallot before operations in the latter condition are considered. That cases with rudimentary spleens also may mimic an uncomplicated Tetralogy of Fallot, is shown by the two cases of *Donzelot et al.* (1949) and *Doliopoulos et al.* (1952). As mentioned in Part III, these cases masqueraded clinically as examples of Tetralogy of Fallot. Operations resulted in death shortly afterwards. Roentgenologic examination of the abdomen to establish the position of the stomach, the shape of the liver, and a possible asplenia seems advisable in cases of suspected Tetralogy of Fallot to rule out the syndrome under consideration. Minor surgical procedures have been followed by death in three cases. In *Bossert & Leichtentritt's* (1920) case death followed an adenoidectomy, the cause of death being meningitis. In *Kimura* (1930) case incision of an atretic anus resulted in death shortly afterwards. In Case 6 of *Campbell et al.* (1953) death followed a tonsillectomy that was performed before a planned shunt operation.

A persistently increased number of Heinz bodies in the peripheral blood has been stressed by *Gasser & Willi* (1952 and 1955) to aid in the diagnosis of this syndrome. They also found Howell-Jolly bodies in their cases (1955). It should be pointed out, however, that Heinz bodies by no means occur only in cases of asplenia, but may be found, for example, after administration of various benzene compounds, and in certain hemolytic anemias (*Hartnauer*, 1953; *Dacie*, 1951). Heinz bodies have also been produced experimentally

after administration of methylene blue (*Spicer & Thomson, 1949*). In none of the new cases presented, were Heinz bodies looked for clinically. They are destroyed by most fixatives (*Dacie*).

In relation to etiology of asplenia, the teratologic syndrome of visceral symmetry, it may be mentioned that there was no known instance of any of the mothers' being exposed to rubella, nor was there any family relationship among the 14 new cases presented. There is in the literature a very slight suggestion that there may be a familial occurrence. *Polhemus & Schafer's (1952)* Case 3 is reported to have had a sibling with multiple spleens and congenital heart disease with a common atrio-ventricular ostium at autopsy. *Gasser & Willi (1952)* consider it quite certain that the causative factor is endogenous, a lethal factor with pleiotropic effects. The present material does not give any clues to the etiology.

Summary and Conclusions

Part I. Six embryos measuring 9—12 mms. in greatest length have been shown by the writer to contain early splenic primordia in the left aspect of the dorsal mesogastrium. The embryos belong to Horizons XV—XVII of Streeter, thus their ovulation age is estimated to be 31—36 days. Temporal relations of splenic formation to cono-truncus septation and division of the A—V canal have been discussed. This last is divided before septation of the cono-truncus is completed (Streeter). The author has shown that early splenic primordia exist at the time of fusion of the A—V canal cushions, in Horizon XVI. At the same time there is initiation of pulmonary lobation, and there is a primitive gut mesentery.

Part II. Congenital absence of the spleen (asplenia) is rare. At the Boston Children's Hospital it was found 12 times in an autopsy series comprising 7,032 post-mortem examinations. Eleven of them were associated with congenital malformations of the heart and great vessels. Asplenia associated with malformations may be said to constitute a syndrome. It is suggested by the writer that it be called "asplenia, a teratologic syndrome of visceral symmetry".

Data on autopsy cases of asplenia associated with congenital cardiovascular anomalies have been compiled in this study. Such a selection has been made in order to pick up cases of hearts whose formation may be assumed to have gone astray at approximately the same time, that is, when the spleen should have been formed during embryonic life.

Fourteen new cases of this syndrome are reported, and 55 cases have been collected from the literature. Cono-truncus anomalies occur in 65 of 67 cases of asplenia (97 per cent). There are three types. Type A, persistent truncus arteriosus, contains 10 cases; Type B, pulmonary stenosis or atresia, comprises 41 cases (19 with stenosis and 22 with atresia); Type C, transposition of the great arteries without pulmonary stenosis or atresia, 14 cases. There are two cases, Type D, with normal cono-truncus regions, and two cases without available descriptions of this region. In Type A, four of the cases are the writer's; in Type B, seven (four with stenosis and three with atresia); and in Type C, three cases.

The atrio-ventricular region is abnormal in 56 of 58 cases with adequate

description (97 per cent). These anomalies vary in type; a common A—V ostium is present in 46 cases, or in 79 per cent. Moreover, there are cases of tricuspid atresia or mitral atresia. The two cases with normal cono-truncus had normal A—V regions.

The cardiovascular anomalies are looked upon as due to developmental arrest. Thus, there are 32 cases of *cor biloculare*, and 18 additional cases have defects in the area of the *ostium primum*. In 36 cases there are anomalous pulmonary venous connections, total or partial. In 19 cases there are bilateral superior *venae cavae*. A new classification of this anomaly is proposed. In 46 instances there is abnormal lobation of the lungs; in 40 of these the lobation is symmetric; and in 35, each lung had three lobes. The liver is transposed in 17 cases and symmetric in 31 cases. The stomach is transposed in 33 instances. There is a common mesentery in 33 cases.

Serious infections occurred in a number of cases. They were more common under the age of 10 months. Five instances of meningitis are present in 66 cases of asplenia, including one case without cardiovascular anomalies. These facts are discussed briefly in relation to the occurrence of infections reported after splenectomy in infancy. The incidence of meningitis in congenital heart disease associated with asplenia does not appear to be significantly higher than in such cases with spleens.

Part III. Multiple spleens or rudimentary spleens may occur together with cardiovascular anomalies similar to those encountered in cases of asplenia. Four new cases of this association are reported, and six examples from the literature are mentioned. One additional case of multiple spleens without cardio-vascular anomalies is reported. The significance of multiple spleens and the possibility that this defect occurred later in embryogenesis than asplenia are discussed. The associated cardio-vascular anomalies furnish some support for this possibility. Accessory livers were found by the author in two cases of asplenia. The possibility of confusing an accessory liver with a rudimentary spleen is stressed and discussed.

Part IV. The pathogenesis of the cono-truncus anomalies in cases of asplenia is discussed. There is a statistically significant linkage between the cono-truncus and the A—V region in the present material. All cases with A—V anomalies have malformed cono-truncus regions. All cases with cono-truncus anomalies and adequate description of the A—V regions have malformations of the latter. Two cases with normal cono-truncus have normal A—V regions.

The interrelationship between the cono-truncus and the A—V region is dis-

cussed. There is an unusually high incidence (97 per cent) of abnormal A-V region in linkage with an abnormal cono-truncus region. There is evidence that the A-V canal cushions fuse before the septation of the cono-truncus is complete. This fusion occurs when the spleen is in its early formative stage, in Horizon XVI. The spleen is congenitally absent in all cases. In view of these facts it is concluded that the abnormal A-V region in the cases presented might have been primary to the coexistent cono-truncus anomalies.

Clinically, cases of Type B may mimic an uncomplicated Tetralogy of Fallot. Attempts at surgical anastomoses failed in four cases in this category. This was presumably due to the severe associated defects, and to the pulmonary arteries' being hypoplastic. Minor surgical procedures have caused death in three instances: one after incision of an atretic anus, another after adenoidectomy, and a third after tonsillectomy. Most of the cases fall within the age range of birth to 1 year. Roentgenologic examination of the abdomen to establish the position of the stomach, the shape of the liver and a possible asplenia should aid in the diagnosis of this syndrome.

The etiology of asplenia, a teratologic syndrome of visceral symmetry, has not been discussed. The cases presented do not furnish data for such a discussion.

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Addendum

While this paper was in press *Smyth's* (1955) report on "lateroposition of the atrial appendages" was published. *Smyth* has compiled data on 18 cases of this anomaly, including the four instances mentioned on p. 91. In all 18 cases there was transposition of the great arteries. Thirteen cases had anomalous A—V regions, and four had normal A—V ostia (*Birmingham*, 1892/93; *Ngai*, 1935; *Harris & Farber*, case 12, 1939; *Dixon*, case 2, 1954), as inferred from the original case reports. Most commonly there was tricuspid atresia or stenosis.

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TABLE

the spleen

	Previous operations anterograde	Right aortic arch
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TABLE A¹
The spleen with persistent truncus arteriosus

Type A. Cases of agenesis

	Age	Sex	Levocardia	Dextrocardia	Interrtrial septal defect	Foramen ovale	Persistent ostium primum	Interventricular septal defect	Corn. biventriculare.
Krausse, # 2, 1905	9 d	M		+	+			+	+
Garyin, 1927	?	?		+	+			+	+
Kimura, 1930	3 w	M			+		+	+	+
Shapiro, 1930	14 m	M		+	+			+	+
Gasser <i>et al.</i> , # 1, 1952	11 w	F			+			+	+
Baumann, # 1, 1954	3 d	M		+	+			+	+
Author, # 1	Sb	M	+		+			+	+
" # 2	3 d	M	+				+	+	
" # 3	4 w	F	+					+	
" # 10	5 m	M	+	+				+	

¹ In this and the following three tables: the symbol, +, indicates that the indicates that this feature was not mentioned in the case report.

genesis

Interventricular septal defect

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are shown in a table. Six of the patients had severe cerebral disorders in the form of oligophrenia, epilepsy and, in 4 cases, spastic pareses. Three were blind, 2 had a coloboma of the uvea, and 4 had repeated periods of unaccountable rise of temperature (cerebral fever?). In 5 patients, air-encephalography revealed a considerable cerebral atrophy, also involving the hypothalamic region. Two boys were obese.

Hormone analyses of 24-hour urine showed a slightly increased excretion of 17-ketosteroids and corticoids in most cases. Oestrogenic hormone could not be demonstrated. In 2 patients, one analysis showed an excretion of gonadotrophin >50 M.U., in the other cases it was <50 M.U. Examination of vaginal epithelium stained according to Schorr's method showed infantile cells without oestrogenic influence. The genitals and the height of the patients corresponded to their chronologic ages, whereas the bone age was slightly accelerated in a number of cases. Roentgenologic examination of the pituitary fossa and of the urinary tract (adrenal regions) showed normal conditions.

In 1952 SILVERMAN *et al.* published a series comprising 29 patients (28 girls and 1 boy). The authors had observed a number of the patients until they arrived at the normal age of puberty. Development of the breasts and menarche occurred at the normal time, and none of the girls were virilized.

According to SILVERMAN *et al.*, the cause of the precocious growth of sexual hair may be (1) increased susceptibility of the hair follicles to androgenic hormone, and (2) increased secretion of adrenal androgens. The first explanation is purely theoretical, whereas both the work of SILVERMAN *et al.* and the present study seem to suggest a slightly increased production of adrenal cortical hormones.

Seven out of the 29 patients reported by SILVERMAN *et al.* were mentally retarded. The authors consider this to be a chance coincidence. In the present series of cases, 6 out of 11 children were deeply oligophrenic. In examinations of 139 children from 2 homes for mentally defective (99 boys <9 years and 40 girls <8 years) the writer found 4, all girls, with premature pubarche. This incidence is not found in a similar number of normal children. Air-encephalography in 5 children with premature pubarche showed diffuse cerebral atrophy which also involved the hypothalamic region. The precocious growth of sexual hair may possibly be explained as being caused by a disturbance in the cerebral regulation of the hormone production of the adrenal cortex, perhaps via the pituitary body.

The considerable preponderance of girls both in the series published by SILVERMAN *et al.* and in the present series may perhaps be explained by a possibly greater susceptibility of the hair follicles of girls to androgens.

Reference

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Testis Biopsy

by HENNING ANDERSEN, MOGENS ANDREASSEN and FLEMMING QUAADE

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The practical purpose of the work was to elucidate the question whether it will be permissible to postpone the operation for cryptorchism to the age towards puberty as is now the common practice in most countries.

In connection with orchidopexy, biopsy of 30 testes in all from boys at ages from 6 to 14 years was therefore performed. On the basis of the genital development and secondary sex markings the patients were classified as being in full puberty +; in early puberty (+), or not in puberty (0). Urines from a number of the patients were analysed for 17-ketosteroids and gonadotrophins. In the case of pre-operative treatment with chorionic gonadotrophin (physex) the time interval between the discontinuance of the therapy and the operation is given.

The biopsy technique is shown diagrammatically at the exhibition. The histological picture was evaluated on the basis of biopsies of normal testes, and classified according to Talbot as infantile, prepuberal and puberal.

None of the testes examined, whether retained or ectopic, were found to be definitely degenerated. The testes of patients treated with physex did not differ from those of the other boys.

To elucidate conditions after puberty, the results of 3 testis biopsies from 2 men, aged 17 and 35, (Surgical Clinic D, University Hospital, Copenhagen) are shown. In both cases a severe degeneration of the germinative epithelium was found, in the latter case there was severe peritubular fibrosis as well.

The four last cases differ from the others of this group, as the children, besides cryptorchism, had symptoms of diseases which might be supposed to influence the endocrine function: Encephalopathy with electro-encephalographic signs of hypothalamic lesion; genital aplasia; nanism with infantilism.

Changes of the Spine in Children with Myxoedema

by HENNING ANDERSEN

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There are rather few reports on roentgenologic changes of the spine in myxoedematous children. ROYER and MEGEVAND, 1954, have recently published an extensive survey of the subject, from which it appears that the series of SWOBODA, 1950, and EVANS, 1952, comprising 7 and 13 cases respectively, are the largest.

The change most frequently described is a defect in the upper part of L 2, or the adjoining vertebrae, often associated with kyphosis. Roentgenologically, this finding has been demonstrated as early as at the age of 9 months (EVANS). The deformity has been compared by several authors with similar findings in chondrodystrophy, Hurler's and Morquio's diseases.

In his text-book of 1945, CAFFEY drew attention to the fact that the myxoedematous spine is retarded, and he illustrated two cases, aged 3 and 8 years, presenting flattened vertebrae, large intervertebral spaces, persistent anterior vascular depression of foetal shape, and open neurocentral synchondrosis. BAMATTER, 1947, described the spine of a severely myxoedematous girl, aged 13, who presented platyspondylitis, wide intervertebral distance and increased distance between corresponding articular processes.

Writer's investigations.—Since January, 1953, X-rays have been regularly taken of the spines of myxoedematous children in the clinic. In a number of cases, previous X-rays were available for comparison. In estimating possible retardation, importance was attached to the above-mentioned findings which were compared with conditions in a number of normal children at the same ages, but of different build. As the variation in the normal development is greatest in the youngest children, and as the present series is so small, the degree of development was not estimated in these cases.

The examination comprised 14 children with unquestionable myxoedema, estimated according to the classic criteria, including the effect of thyroid extract.

The children were divided into two groups according to the intensity of the thyroid medication prior to the time when the first roentgenogram of the spine was taken:-

- (1) Cases 1-10, untreated or insufficiently treated.
- (2) Cases 11-14, satisfactorily treated.

Roentgenograms and a table giving the duration of treatment, the bone age and the degree of epiphyseal dysgenesis, compared with the findings in the spine, are shown at the exhibition.

Result of examination.

In the group of untreated or insufficiently treated children, spinal changes were found in all 10 cases.

Retarded development with platyspondylisis, wide intervertebral spaces and persistent anterior venous depression of foetal or infantile shape as the most constant and distinctive findings were demonstrated in all the children except two infants in whom, as already mentioned, conditions could not be estimated with certainty.

In two infants of this group, aged 3 1/2 and 4 1/2 months, changes were demonstrated in the corpora of the vertebrae; these changes were of the same appearance (condensation ring and, later, double contours) as those described by ENGESET, IMERSLUND and BLYSTAD in the case of the short bones of the extremities, and were present also in the ossification centres of the tarsus in these cases. Serial X-rays showed that the changes in the corpora and the tarsus appeared and disappeared at the same time in the course of treatment with thyroid extract.

Isolated defects in the lower thoracic or upper lumbar vertebrae were present in 4 cases.

In Case (2) the changes were demonstrated at a very early age (4 1/2 months). Case (3) has been observed for 6 years; in spite of intense treatment, the change can still be demonstrated. In Case (9) there was a bracket-like projection on the anterior surface of L 1 in addition to defects in TH 12.

In patients (9) and (10), absence of calcification of the borders of the vertebrae and abnormal structure of the corpora were also ascertained. These patients were brothers with myxoedema that had been diagnosed late; their case histories have been previously reported by ØSTER.

The cases of myxoedema that had been satisfactorily treated had normal spines, and the bones of their extremities were normal. The last two cases (13) and (14) were late-developed forms of myxoedema.

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Nutrition

Einwirkung verschiedener Faktoren auf die Dauer der Stillzeit

Zusammengefasst an Hand von Erhebungen an der städtischen Mütterberatungsstelle Stockholm

von PER J. NORDENFELT

Das hier verarbeitete Material erfasst die Hälfte der 1950 an der Mütterberatungsstelle Stockholm eingeschriebenen Kinder, d. h. 4003 Fälle, wovon 3806 eheliche und 197 uneheliche.

39,0 % der Mütter hören mit Stillen auf, bevor das Kind 6 Monate alt ist, und 39,7 % konnten sechs Monate oder länger, ohne dauernde Zugabe anderer Nährmittel selbst stillen.

Ledige Mütter stillen ihre Kinder weniger lang als verheiratete.

8,6 % der Mütter gehen vor Ablauf von 6 Monaten beruflicher Arbeit ausser Hause nach, und zwar 37,1 % der Ledigen und 7,2 % der Verheirateten. Die Berufssarbeit verkürzt die Stillzeit um ein Beträchtliches.

Mütter unter 25 Jahren stillen am wenigsten lang; ältere, über 35 am längsten.

Je höher die soziale Schicht, der die Mütter angehören, desto länger die Stillzeit.

Allgemein wird das Erstgeborene am besten gestillt, die Folgenden ziemlich gleichmässig.

Kinder, die bei der Geburt weniger als 3000 g wogen, werden weniger lang gestillt als die anderen.

In engen Wohnverhältnissen (mehr als 2 Personen pro Wohnraum) lebende Mütter stillen etwas weniger lang, als solche die über mehr Raum verfügen.

Am genauesten sind die medizinischen Ursachen für eine verkürzte Stillzeit festzustellen; sie umfassen in vorliegendem Material 11,9 % Mütter und 3,4 % Kinder.

The Effect of Raw Certified Milk and Ordinary Pasteurized Milk on the Growth and Health of Two Uniform Groups of Infants

by HAAKON NATVIG and LARS GRAM

*Oslo City Board of Health, Department of Food-Inspection; The Institute of Hygiene,
University of Oslo; Akeberg Nursery Home.*

By examination of two uniform groups of infants of which the one group had been fed on milk formulas made of raw certified milk and the

other group had been fed on milk formulas made of ordinary pasteurized milk the following results were obtained:

There was no difference in the increment of length or weight, no difference in the general condition, nutrition or dentition and no difference in the number of cases of alimentary anemia or dyspeptic conditions. The examination disclosed no significant difference between the two groups of children in the nature, frequency, course or duration of infectious diseases. The duration was calculated on the basis of the number of days with fever in proportion to the total days of stay in the nursery home.

By bacteriological and chemical examination of the milk it was found that both kinds of milk were of a high hygienic standard and there was no important difference in the bacteriological-chemical composition of the two brands of milk.

The article is to be published in *Acta Paediatrica Scandinavica*.

On the Incidence of Breast-feeding in Helsinki 1952

by NIINO HALLMAN, HEIKKI KALLIALA and LEENA TUUTERI

Children's Clinic, Helsinki

The material was collected with the help of the district nurses using questionnaires. It consists of 2,597 infants, i.e. nearly 50 per cent of all infants born in 1952 in Helsinki. Less than half of the infants were fed with breast milk at the age of 3 months and less than one-fifth at the age of 6 months. Compared with previous statistics from Helsinki the incidence of breast-feeding has decreased.

Such factors as the social position of the family, the age, the parity and the constitution of the mother and household help during pregnancy and lactation do not seem to have any certain influence in our material. The lactation period was somewhat shorter in the cases where the family lived in overcrowded conditions.

The cause of the early weaning was said to be illness of the mother or infant in one-fifth of the cases, and mother's occupation in one-tenth of the cases. In 50 per cent of the cases no cause could be given. The results suggest that the mother's attitude towards breast-feeding is more important than any other single factor.

Allergy

Age and Sex Variations of Cutaneous Reactions in Asthmatic Children

by E. WINGE FLENSBORG

*Municipal Out-Patient Clinic for Allergic Diseases in Children, Copenhagen
(Physician-in-Charge: E. WINGE FLENSBORG)*

Scratch tests with a considerable number of allergens (house dust [purified], feathers, various animal hairs, clothing textiles, foodstuffs, tree pollen, grass pollen, flower pollen and various moulds) were carried out in all children with the diagnosis of bronchial asthma and/or asthmatic bronchitis who have passed through the Clinic, viz. 853, of whom 573 boys (67 per cent) and 280 girls (33 per cent).

Only definitely urticarial, sharply and irregularly delimited immediate reactions were registered as positive.

Very considerable variations in the positivity of the cutaneous tests as regards age and sex were demonstrated.

For the great majority of allergens, the frequency of positive cutaneous tests increased with increasing age. The most marked increase was observed with house dust (from 1-2 per cent of the children in the two first years of life to 64 per cent of the children aged 12-15 years); feathers come next with an increase attaining 50 per cent in the age group 12-15 years.

A varying increase (from zero to a few per cent during the first years of life) was demonstrated in the various tests with animal hairs (cow hair up to 20 per cent, cat hair up to 18 per cent, horse dandruff up to 16 per cent, dog hair up to 11 per cent) with pollen (grass pollen up to 22 per cent, flower pollen [*compositae*] up to 18 per cent, tree pollen up to 13 per cent) and with moulds (up to 9 per cent).

As regards foodstuffs, conditions appear to be different, as when eggs were concerned, the frequency of positive cutaneous reactions decreased with increasing age (from approximately 7 per cent in the first two years of life to 4 per cent in the age group 3-5 years, 1 per cent in the age group 6-8 years and 3 per cent in the age group 9-15 years). Similar conditions were found when cow's milk was concerned while the frequency of the positive cutaneous reactions to fish appears to be constant through childhood.

Quite pronounced differences between boys and girls were observed in the cutaneous positivity. Boys react positively more frequently than do

girls and this holds true for all age groups and for the majority of the allergens. This is most marked when house dust and feathers are concerned.

From a purely practical point of view, the above findings indicate that it is insufficient to let asthmatic children undergo one single cutaneous testing only and subsequently base the treatment upon the result of this. Ideally, asthmatic children should be tested annually or at least as frequently as is indicated by possible unsatisfactory condition during treatment.

Provocation Experiments in Asthmatic Children

by K. DAMGAARD

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As a positive cutaneous reaction indicates only that the patient is allergic but not that the allergen concerned is the causal agent of his symptoms, provocation experiments should be carried out as far as possible in order to attempt to separate the manifestly allergic patients from the latent allergic patients.

In the above Clinic, four types of provocation experiments are, as a rule, employed: (1) Natural exposure, (2) inhalation experiments, (3) the sniff test (nasal test), and (4) oral provocation with foodstuffs.

In the present paper, an account is given of the inhalation and sniff tests in 512 patients with asthma and/or asthmatic bronchitis with positive cutaneous reactions to one or several allergens. A total of 1,943 provocation experiments were carried out of which 1,163 were inhalation experiments and 770 were sniff tests. For technical reasons, only children under 3 years of age were examined.

Out of the 512 children, 62 per cent reacted positively on one or several provocation experiments with one or several allergens. With increasing age, a slightly increased inclination to react positively in the provocation experiments to one or several of those allergens, to which the child concerned showed a positive cutaneous reaction, was observed.

Out of the total number of 1,934 provocation experiments (one or several in each child), 43 per cent were positive. No definite age variation appears to exist in this connection.

More detailed analysis of the incidence of positive provocation experiments employing the most important allergens in various age groups does not reveal any typical tendency.

Great variation in the positivity of the separate allergens was noted (all

age groups taken together). Highest percentages of positive reactions were obtained by provocation with horse dandruff (73 per cent), grass pollen (54 per cent) house dust (52 per cent) and moulds (52 per cent).

This corresponds well to the clinical observation that these allergens may be regarded as particularly potent allergens with which pronounced positive cutaneous reactions are most frequently obtained and with which the frequency of general reactions during desensitization treatment is highest.

In 430 cases (in 254 children), sniff tests as well as inhalation tests were carried out with the same allergen in the same period. Among the positive provocation experiments, 39 per cent were positive in sniff as well as in inhalation experiments; 30 per cent were positive in inhalation experiments only and 31 per cent were positive in sniff tests only, i.e. both types of provocation experiment should be employed concurrently.

Good agreement exists between the information in the case-history concerning hypersensitivity towards an allergen and the result of the provocation experiment with the same allergen. When the case-history indicates allergy, 80 per cent of the provocation experiments were positive; when suspicion of allergy is aroused, 45 per cent were positive and when the case-history does not indicate allergy, 38 per cent were positive.

Similarly, an undoubtedly relation exists between the strength of the cutaneous reaction and the result of the provocation experiments. On scratch reaction (+) 24 per cent of the provocation experiments were positive; when the strength of the reaction was +, 38 per cent; ++, 53 per cent and +++, 60 per cent. This condition was found in all allergens examined.

The criteria for positive provocation experiments are shown in tables. It appears from these that the most powerful reaction, the asthmatic attack, is encountered virtually exclusively in patients with ++ and +++ scratch reactions.

The conceptions manifest and latent allergy to a certain allergen must not be interpreted as clearly separated conditions, for a number of different factors (other genuine allergic conditions, infectious allergy, mental and climatic conditions etc.) may determine whether the patient at the time of investigation reacts with clinical symptoms on exposure to the allergen.

The question whether the incidence of manifest allergy increases with increasing age cannot be answered with certainty by the present material; conditions may even vary with the various allergens.

Provocation experiments were repeated in 59 children at a 1-4-year interval with the same allergen once or several times. During this period, transition from latent to manifest allergy to one or several allergens probably took place in 22 of these children (37 per cent).

It is stressed that great care must be exerted in the conduct of provocation experiments. When a powerful general reaction might be anticipated, inhalation experiments are recommended in preference to sniff tests, as the dosage in inhalation is easier to graduate. Particular care should be exerted with patients with powerful cutaneous reactions to animal hair (in particular horse dandruff), pollen and moulds. Adrenaline should always be available.

Prematurity

Milk Drip Via an Indwelling Naso-gastric Tube in the Feeding of Premature Infants

by K. HOLMDAHL

Children's Clinic, Gothenburg, Sweden

Nourishment was administered to the premature infants via a rubber catheter (Nélaton No. 6) by a slow drip which continued during the greater part of the 24 hours. The calculated quantity of nourishment was divided into 3-4 portions. The tube was allowed to remain in situ in the same nostril for approximately 2 weeks after which it was changed to the other nostril.

Since 1952, this method was employed routinely when tube feeding was indicated and 72 premature infants are concerned to date. The total number of tube feeding days to date is 1,500. Some infants have been tube-fed until the age of 2-3 months.

The experience gained from the method which was demonstrated at the Exhibition in tabular form may be summarized as follows:

1. Vomiting and attacks of cyanosis occur despite this form of tube feeding. Vomiting is, however, not so frequent. Aspiration occurred undoubtedly in a couple of cases.

2. Apart from increased secretion of mucus and some swelling of the nasal mucosa in a number of cases, no local complications from the mucous membranes occurred which could be attributed to the nasal tube.

3. The mortality among the premature infants has fallen considerably. The improved results in the lowest weight group are particularly noteworthy. Since 1952, 5 infants with birth weights under 1,000 g (2 lbs. 3 oz.) have survived as compared with only 2 surviving infants in the period from the opening of the Department in 1940 until 1952. The mortality after survival for the first 48 hours has fallen more than has the mortality during the first 2 days of life. The difference is, however, not significant

here and even if it were, no conclusion can be drawn from this as regards the value of tube feeding. Other changes in the care of premature infants have been instituted during the same period.

4. The method has other advantages. The administration of nourishment can be instituted earlier and greater quantities of nourishment be supplied. Handling of the infant is reduced. When oxygen therapy in an incubator is employed, the bottles of the drip apparatus may be replaced outside the incubator so that the concentration of oxygen may be maintained more constant. Time is saved in feeding the infant and this method of feeding may be carried out by less trained personnel.

Retrorenal Fibroplasia in Premature Infants and Its Relation to Oxygen Therapy

Illustrated by a Material From a Danish Premature Ward

by P. BRÆNDSTRUP and E. WINGE FLENSBORG

Children's Hospital, Martinsvej, Copenhagen, Denmark
(Physician-in-Charge: E. WINGE FLENSBORG)

Since July 1950, systematic ophthalmoscopic examinations in view of the incidence of retrorenal fibroplasia (r.f.) were undertaken. Originally only premature infants with birth weights under 1,500 g were examined while later this examination was carried out in all premature infants with birth weights under 2,000 g. The frequency of examinations has been increasing.

A total of 204 premature infants were examined with the following distribution as regards weight groups:

$\leq 1,000$ g (2 lbs. 3 oz.),	3 infants
1,001–1,500 g (2 lbs. 3 oz.–3 lbs. 5 oz.),	78 infants
1,501–2,000 g (3 lbs. 5 oz.–4 lbs. 7 oz.),	123 infants

From two tables in which the results of the total number of ophthalmoscopic examinations and the relation to oxygen therapy were registered the following appears:

- 1) 81 premature infants with birth weights $\leq 2,000$ g received no oxygen therapy whatsoever. All ophthalmoscopic examinations (195) carried out in these infants showed normal conditions.
- 2) 42 premature infants with birth weights $\leq 2,000$ g received oxygen therapy for 1–4 days. All ophthalmoscopic examinations (127) of these infants showed normal conditions.

3) 76 premature infants with birth weights $\leq 2,000$ g received oxygen therapy for 5 days or more (maximal individual duration of treatment with oxygen was 63 days). *Varying degrees of retrorenal fibroplasia were demonstrated in 26 of these infants. In 14 of these cases the condition was reversible, while in 12 it was irreversible.*

Expressed as histogram, the relation between the incidence of r.f. and the duration of oxygen therapy is demonstrated in greater detail. Among other things, it appears from this that:

4) Among 59 premature infants $\leq 2,000$ g who received oxygen therapy for 5–29 days, irreversible r.f. developed in 6 (10 %)

5) Among 17 premature infants $\leq 2,000$ g who underwent oxygen therapy for more than 30 days, irreversible r.f. developed in 6 (35 %).

A more detailed analysis of the onset of r.f. in the present material shows:

6) Changes due to r.f. do not occur during oxygen therapy when this is carried out continuously nor during the initial phase of intermittent oxygen therapy.

7) r.f. is frequently demonstrated immediately after discontinuation of oxygen therapy.

8) Relation may exist between the duration of oxygen therapy and the onset-time of r.f. (in relation to the discontinuation of the oxygen therapy): the shorter the duration of oxygen therapy, the later the onset of r.f. changes.

9) In the present material, r.f. did not develop later than on the 27th day after discontinuation of oxygen therapy.

Demonstration of all slighter, reversible cases of r.f. require very frequent examinations as they frequently are of very short duration. The present material is therefore suitable for analysis of the irreversible cases only.

Such an analysis was carried out in relation both to the duration of oxygen therapy and the degree of prematurity (birth weight) and revealed:

10) Among 36 premature infants with birth weights $\leq 1,500$ g who received oxygen therapy during 0–15 days, none developed irreversible r.f.

11) Among 31 premature infants with birth weights $\leq 1,500$ g who received oxygen therapy during 15–63 days, 8 developed irreversible r.f. and of these 5 became blind.

This appears to indicate that the duration of oxygen therapy rather than the degree of prematurity is decisive in the development of r.f.

Until January 1952, all premature infants with birth weights under 2,000 g were treated liberally with oxygen until a weight of 2,000 g was attained. During this period, 71 premature infants were examined in whom 13 cases of r.f. were demonstrated, 5 of which were irreversible.

For a short period, every alternate premature infant was treated with oxygen but since June 1, 1952, oxygen has been administered in this Department only in emergencies and during this period only 2 mild (reversible) cases of r.f. were demonstrated among 82 premature infants.

During the same period (1952-54), 66 premature infants admitted to the Department from elsewhere had been treated with a reduced oxygen régime with stepping down of the oxygen percentage. Ten of these infants developed r.f. and out of these, 6 were irreversible.

12) It appears from the above, that a drastic reduction in the employment of oxygen in a department for premature infants, so that oxygen is administered only in emergencies and for as short a period as possible, reduces the incidence of r.f. considerably whereas a moderate reduction in the oxygen therapy even when this is terminated by stepping down of the oxygen percentage does not involve any demonstrable decrease in the incidence of r.f.

13) We are of opinion that no direct toxic effect of the oxygen comes into consideration as still active cases of r.f. were «treated» with oxygen in this Department as well as elsewhere whereby the changes in a number of cases regressed.

14) The mortality among premature infants with birth weights 1,001-1,500 g admitted to this Department during the first 24 hours of life was as follows: During the period of liberal oxygen administration, 32 per cent. During the period of oxygen administration in emergencies only, 33 per cent.

Conclusion

Retrorenal fibroplasia is an artificial condition which develops in premature infants as a retinal reaction following oxygen administration (relative anoxaemia).

Oxygen should be administered to premature infants in emergencies only and for as short a period as possible.

Prevention of Retrorenal Fibroplasia

by HILDA BLIX

Children's Clinic, Gothenburg, Sweden

Since November 1950 all premature babies in Gothenburg have had a funduscopic examination once a week until discharge. After that they were kept under control until the age of 6 months. During the first years

4 premature babies had early retrorenal fibroplasia changes. We tried vitamin E and ACTH without success. The changes advanced to a cicatricial stage.

Since July 1952 we have tried to prevent retrorenal fibroplasia according to Szewczyk, by giving oxygen in as low a concentration as possible and for as short a time as possible. We also have weaned the babies from oxygen gradually before it was withdrawn. During this time 59 children with birth weights less than 1,750 g were discharged. None of them had retrorenal fibroplasia at the age of 6 months.

In earlier years (1946 until June 1952) premature babies had been treated with oxygen in incubators, often for a long time and at high concentration before the oxygen was suddenly withdrawn. Among the 199 children with birth weights less than 1,750 g so treated, 12 had retrorenal fibroplasia in a cicatricial stage. Among 34 children with birth weights less than 1,350 g, 7 had the disease. All children with retrorenal fibroplasia have got oxygen in incubators for more than 3 weeks. Seven of them had at least one funduscopic examination in the newborn period and all had normal fundi while under oxygen. The 4 latest cases were followed with funduscopic examination for at least two months. These children had wide and tortuous retinal vessels for the first time 1-2 weeks after oxygen had been withdrawn. In spite of the restricted oxygen administration during the last years, one child with a birth weight of 2,420 g came for control 5 weeks old with fully developed retrorenal fibroplasia. This child had never been given oxygen and was discharged with normal fundi one week old. After that the child had a respiratory infection.

According to Szewczyk, retrorenal fibroplasia is anoxic in character, either because of a sudden withdrawal of oxygen at high concentration or as a result of respiratory infection or general disease which suddenly interferes with the oxygenation. Our experience supports this theory. It seems to be possible to prevent retrorenal fibroplasia due to oxygen administration, but it has not been possible to prevent cases due to a disease which suddenly makes the child asphyctic.

A Follow-up Examination of Small Premature Infants at School Age

by H. BLIX and K. HOLMDAHL

Children's Clinic, Gothenburg, Sweden

Seventy-four children with birth weights less than 1,750 g (4 lbs. 2 oz.) who had been hospitalized in the Department for Premature Infants in

Gothenburg during the years 1940-46 and all of whom had attained the official school age (the calendar year in which the child attains 7 years) were examined in view of scholastic attainments and physical development. If the children had siblings, the scholastic attainments were compared with theirs, premature siblings being excluded. Among the premature children, 41 had siblings.

The result of the investigation, which was demonstrated in tabular form, may be summarized as follows:

1. Children, born prematurely, experience greater difficulty in school than do their contemporaries and this takes the form of postponement of school attendance, failure to advance to the next class or the necessity of attending special classes on account of mental retardation. The difference is statistically significant for the entire group as well as for the group with birth weights 1,510-1,750 g (3 lbs. 5 oz.-4 lbs. 2 oz.).

2. Children born prematurely require education in institutions for mental defectives or in schools for educationally retarded children to a greater extent than do their siblings. The difference is significant for the entire group and probable for the group with birth weights of 1,510-1,750 g.

3. The school reports in the academic subjects are somewhat poorer when children are born prematurely and attend the normal classes in primary schools but this difference may be random. For physical culture, conduct and discipline, the reports were approximately the same.

4. No difference could be demonstrated as regards weight and height.

5. Out of the 33 children, born prematurely, who had no siblings, 13 experienced difficulties at school in the forms mentioned above.

6. Out of the 5 children who suffered from severe attacks of cyanosis or in whom considerable feeding difficulties were experienced while in the Department for Premature Infants, 3 attended classes for educationally retarded or for educationally subnormal children.

Cardiovascular System

The Heart and Circulation in Funnel Chest

by Å. GYLLENSWÄRD and H. LODIN

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A marked degree of funnel chest produces pressure on the heart, which is partly compensated by rotation and sinistro-position. The series of pressure curves and angiograms presented shows that in many cases

there exists however considerable deformity of the right ventricle and pulmonary artery in particular, with simultaneous increase in pressure in the pulmonary circulation. After operation the heart and pulmonary circulation are normalized. The authors are of the opinion that investigations of this type make it possible to select those cases of funnel chest which apart from cosmetic considerations, require surgical correction.

Haemangioma in Premature and Full-time Newly Born Infants

by K. HOLMDAHL

Children's Clinic, Gothenburg, Sweden

The term haemangioma as employed in the present paper, indicates hypertrophic endothelial haemangioma. Such tumours are situated superficially and grow more rapidly than does the surrounding tissue. As a result, they become more or less raised above the skin surface and therefore assume the characteristic strawberry-like appearance.

Capillary haemangioma (so-called telangiectases) and the more deeply situated cavernous haemangioma are thus not included in the investigation.

The primary material consists of 293 premature infants with birth weights of under 2,000 g (4 lbs. 7 oz.), 347 premature infants with birth weights between 2,010 and 2,500 g (4 lbs. 7 oz.-5 lbs. 8 oz) and 186 full-time infants. In the majority of cases, these infants were examined regularly for the occurrence of haemangioma until the age of 6 months. In a number of cases, the period of observation was even longer.

The result, which was demonstrated at the Exhibition in tabular form, may be summarized as follows:

1. The tendency to formation of haemangioma seems to be equal all over the skin surface.
2. Haemangioma are very rare at birth and develop, as a rule, during the second to fourth week of life.
3. The risk of developing haemangioma is perhaps somewhat greater in the smallest premature infants during the first three weeks of life but the difference is not significant.
4. The final risk of developing haemangioma is the same both for premature and for full-time infants (approximately 12-13 per cent at the age of 6 months).
5. On account of this tendency to proliferation in the vascular system, which is most pronounced during the second to fourth week of life, as ex-

pressed by haemangioma, these demand interest from more than a cosmetic point of view: they constitute an interesting biological problem.

6. As haemangioma are as common in full-time infants as in premature infants in the various weight groups, one of the arguments for a connection between haemangioma and retrosternal fibroplasia is excluded.

7. Haemangioma show a spontaneous tendency to regress during the second six-month period of life.

Infections

Results of 181 Tuberculous Meningitis Cases, Treated in 1949-1954

by OLE WASZ-HÖCKERT

Childrens Clinic, Helsinki, Finland

181 cases of tuberculous meningitis, 47 of them with miliary TB and meningitis, are reported. Cases treated more than 2 months in other hospitals are not included in this material.

Table 1
Methods of treatment

Treatment groups	SM		PAS perorally g/kg/day	Isoniazid		Cortisone	
	Dihydro-streptomycin sulfate intramus. mg/kg/day	Streptomycin sulfate intrathecal		Tabl. perorally mg/kg/day	Solution intrathecal mg/kg/day	Tabl. perorally mg/kg	Hydrocortisone solutions intrathecal mg/kg
I	100→50	25 mg i.lumb.	—	—	—	—	—
II	50→25	1-3 mg/kg ¹	0.3	—	—	—	—
III	30→20	»	»	5	0.5	—	—
IV	20→10	»	»	10	»	2	1

¹ 1 mg/kg for 7-15 year olds
 2 » » 3-6 » » } half these doses were given in suboccipital and intraventricular injections
 3 » » 0-2 » » }

20 of the children were 0-1 year of age, 64 between 1-2 years. Only 12 patients came in the 10-15 year age group.

Table 2
Results of treatment

Treatment group	Cases	Recovered	Died	Time of treatment (mean)	Time of after-observation (mean)
I	17	5	12 (70 %)	8 months	4 years
II	103	53	50 (48 %)	6 $\frac{1}{2}$ "	3.2 "
III	37	26	11 (29 %)	6 "	1.6 "
IV	24	20	4 (15 %)	5 "	5 months

It must be noted that the patients come to the Children's Clinic from all over the country (up to 950 km), and this is a reason why cases are often admitted too late. Thus 7 children died within 72 hours and a further 31, 0-13 days after admission. If these 31 essentially hopeless cases were excluded from the material, the death rate would be 30.6 per cent. It should also be mentioned that all the cases are of human strains. Bovine TB does not exist in Finland.

Complications: Relapses 4, deafness 12 and hardness of hearing 4 cases. The high blockage in the CSF-system is the most dangerous complication. Every known method of treating high blocks has been used (streptokinase, over-compression, PPD, tryptar), but trepaning and ventricular drainage with permanent catheter still seems to be the best method (8 out of 40 trepaned cases recovered). Hydrocortisone intrathecally seems to prevent the onset of high-blockages. (See also: WASZ-HÖCKERT: Nord. med. 51: 101, 1954.)

Are Children Not in the Care of Their Mothers More Susceptible to Acute Infectious Illnesses than Children who are in the Care of Their Mothers?

by RUTH WEGELIUS and MIRJAM LINKOMIES

Pediatric Dept., Maria Hospital, Helsinki, Finland

Among 511 children who during the months of January and February 1954 were examined in the Out-patient Ward of the Ped. Dpt. of Maria

Hospital, Helsingfors, no difference was observed in the frequency of acute infectious illnesses in children who went to Kindergartens and similar institutions and children who stayed at home with their mothers.

Interstitial Plasma Cell Pneumonia

by E. K. AHVENAINEN, N. HALLMAN, P-E. HEIKEL, HILKKA TÄHKÄ,
ANNELI YLINEN and ARVO YLPPÖ

Children's Clinic, Helsinki, Finland

About 200 cases of interstitial plasma cell pneumonia have been treated at the Children's Clinic of the University of Helsinki and at the Children's Castle in 1949-52. Most of these patients are premature babies or infants recovering from a serious disease. About 30 of them are full-term infants who have been treated in an institution, because of their mothers' active pulmonary tuberculosis.

The typical picture of the disease shows lack of appetite, arrested gain in weight, rapid and difficult breathing. The temperature was, however, usually normal. In the blood, erythrocytes and reticulocytes often increase as well as plasma calcium and non-protein nitrogen. In urine there is often protein and the urinary sediment reveals leucocytes, erythrocytes, epithelial cells and sometimes granular or hyaline casts. All these symptoms return to normal during the recovery which takes some weeks. The mortality was in this material in the first years about 60 per cent and later on about 20 per cent.

47 patients have been examined 1 1/2-5 years after the disease. Four of them have a continuously high plasma calcium and non-protein nitrogen, and are mentally and physically retarded. Their skulls and skeletal bones show osteosclerosis.

An autopsy was performed on all the patients who died in the acute phase of the disease. The lungs showed grossly and microscopically interstitial plasma-cell pneumonia and the kidneys revealed signs of "lower nephron nephrosis" and calcium crystals.

Rubella During Pregnancy

by ROLF LUNDSTRÖM

Kronprinsessan Lovisa's Children's Hospital, Stockholm, Sweden

The Poliomyelitis Epidemic of 1953 in Stockholm and the Rest of Sweden

Management of Poliomyelitis Cases and Technical Equipment Required

by JUSTUS STRÖM and ELIAS BENGTSSON

Infectious Diseases Hospital, Stockholm, Sweden

The organization of the National Poliomyelitis Association of Sweden and of an infectious diseases hospital is schematically described, with special reference to the use of respirators in acute cases.

The epidemic of 1953 is shown in figures and tables: seasonal variation, geographical distribution, age and sex incidence of different paralytic forms, therapeutic results in severe cases, mortality in various forms of artificial respiration, etc. One noteworthy finding is that the incidence of paralysis shows a maximum between the ages of 20 and 35, and that the relative incidence of severe cases with respiratory and pharyngeal paralysis continues to rise steeply in males, but not in females, after that age. The importance of larger units at the treatment centers is illustrated by the fact that the major centers had a substantially lower mortality than the small units in the provinces.

A tabulation is presented of the technical equipment required in a department for acute respiratory cases, together with a description of wards and nursing departments, and a formulation of the desiderata as to the capacity of different laboratories. Figures and data are given showing the design and principles of the different types of respirators in use in Sweden today.

Neurology

The Normal Electroencephalogram in Infants and Small Children

by STEN BILLE and SVEN BRANDT

Queen Louise's Children's Hospital, EEG Unit, Copenhagen, Denmark

The normal material has been collected from over 100 healthy children, 0 til 6 years of age, without known cases of epilepsy in their families and who themselves have never suffered severe head injuries or had seizures of any kind.

Part of the exhibition should offer a practical solution to the question: "How to get a quick and still safe impression of the dominant frequency in a child's waking record?" For this purpose 10 seconds' cut-outs have been taken from 10 different children within each age group. These 10 cut-outs have been arranged underneath each other on cartoons, that can be folded together as a book. The following age groups have been used: 0-3, 4-6, 7-12, 13-18, 19-24 months. Further: 2-2 1/2, 2 1/2-3, 3-4, 4-5 and 5-6 years.

For each age group two folding books have been made, named A and B. In A are demonstrated typical average dominant rhythms. For B the most extreme variations from the average frequency in respect to potentials of longer durations have been chosen, mostly from periods of definite waking phase, sometimes from periods questionable of slight drowsiness.

The EEG of a child to be examined can quickly be compared with models from the corresponding age group. The method offers information not alone about the variation among different children of each age group but also—by comparing A and B models—about the occasional individual fluctuations found under normal circumstances.

Another part of the exhibition demonstrated EEG-changes during drowsiness and sleep which may be mistaken for specific epileptic abnormalities.

Among 136 healthy children four showed EEG patterns which had to be classified as definitely abnormal (about 3 per cent).

Electroencephalographic Findings in Children with Febrile Convulsions

by RAGNHILD BJERGLUND and SVEN BRANDT

Queen Louise's Children's Hospital, Seizure Unit, Copenhagen, Denmark

An abnormal EEG was found in 25 per cent of 129 children with one or more epileptic seizures exclusively in relation to temperature rise. Abnormalities were most frequent in females and among children aged 3-4 years. The frequency was highest in the group with more than one seizure, slightly higher following seizures of long duration than after seizures of short duration. Not higher in children examined shortly after the attack compared with those examined after a longer interval. Abnormalities may disappear with time, may persist unchanged or may exaggerate. A few children with normal EEG from the start may show abnormalities after later seizures.

EEG findings indicate that "febrile convulsions" are actually epileptic seizures although for the most part caused by a mild form of epilepsy with a fairly good prognosis. On the other side, not a few adult patients with persistent epilepsy had their first epileptic manifestations in early childhood as febrile convulsions. EEG offers a better chance to screen such cases for early and sufficient antiepileptic treatment.

Some Figures to Throw Light on Aetiological Factors in a Cerebral Palsy Material of Altogether 320 Patients

by MARIT SKATVEDT

Children's Hospital, Rikshospitalet, Oslo

1. Weight at birth known in 266 cases

Among 94 patients with bilateral spastic paresis 50 per cent had a birth-weight under 2,500 g. In the rest of the material 16 per cent weighed under 2,500 g and 16.2 per cent over 4,000 g. If the patients weighing under 3,000 g are ignored, 26.9 per cent of the patients weighed over 4,000 g. (In a normal material consisting of 2,060 infants, the corresponding percentage was 17.9.)

2. The course of delivery in 301 cases

59 per cent were stated to be normal, 41 per cent to be pathological. In the ataxia group 9 out of 16 patients had a pathological delivery, and this was so in 48 per cent of the cases of hemiparesis, in 45 per cent of the cases in the mixed group, in 34 per cent of the cases of bilateral spastic paresis, and in 35 per cent of the cases of athetosis. It is remarkable that as many as 41 per cent of the pathological deliveries belonged to the prolonged delivery group.

3. Postnatal aetiological factors

Here asphyxia and signs of injury to the brain during or just after delivery hold a dominating position, being present in as great a proportion as 48 per cent. Kernicterus with Rh incompatibility was found in 4.9 per cent, whereas 4.2 per cent had prolonged and severe jaundice without Rh incompatibility. In 10.5 per cent there was no demonstrable prenatal, natal or postnatal cause.

On Seasonal Variation in the Galvanic Excitability of Infants in Finland

by ANNikki SEPPÄ-KIVALO

Children's Clinic, Helsinki, Finland

The galvanic excitability of healthy infants, 1 to 12 months old, from a well-baby clinic was determined during one year. A series of 236 galvanic excitability tests made on 158 infants displayed a seasonal variation of galvanic excitability, the sensitivity to galvanic current being highest in the summer and lowest in the winter. It was found that a distinct relation exists between galvanic excitability and ultraviolet radiation of the sun.

As factors connected with galvanic excitability, the plasma total calcium, inorganic phosphorus, and total protein were determined in 90 healthy infants (271 calcium and protein determinations, 210 phosphorus determinations). The ionized calcium fraction was computed from total calcium and total protein. Ionized calcium fraction and inorganic phosphorus were highest in the spring and summer and lowest in the autumn and winter.

The seasonal changes in galvanic excitability cannot be explained by the changes in the ionized calcium fraction. An explanation by means of the changes in phosphorus is possible.

The Cerebral Palsy Treatment Unit at Kronprinsessan Lovisas Barnsjukhus, Stockholm

by K.-M. HERRLIN

Crown-Princess Lovisa's Children's Hospital, Stockholm, Sweden

Kronprinsessan Lovisas Barnsjukhus is now a treatment centre for cerebral palsied children in Stockholm. The major part of the work is carried out at the medical and psychiatric clinics, with their diagnostic and therapeutic resources of various kinds. Every neurological case of the cerebral palsy type is examined and evaluated by the hospital team (paediatrician, neurologist, orthopaedic surgeon, physiotherapist and social worker) and by one of the child psychiatrists. Other specialists are consulted if necessary. The appropriate treatment is then planned. The team continues to supervise the patient at a special out-patient department. This permanent unit, with specialists in the various fields, has been gradually enlarged

since the autumn of 1951. Such a unit is essential if as all-round an evaluation as possible and planning of therapy on this basis are to be realized.

The diagnosis of cerebral palsy is a neurological diagnosis. It is not infrequently difficult to establish, and requires great experience. This applies, for example, to the evaluation of aetiological factors and to the appraisal of the neurological symptoms and the mental development. Of the children brought to our hospital by their parents, or referred by other physicians as cases of cerebral palsy, no less than 16 per cent (23/143) were found to suffer from other developmental disturbances or neurological disorders, in two cases a brain tumour. These figures apply to the period November 1951 to April 1954.

The cause of the brain damage in the 120 children with cerebral palsy (77 boys and 43 girls, aged 0–16 years) was considered to be pre-natal in 23 per cent, natal in 41 per cent, post-natal in 19 per cent and of unknown origin in 17 per cent. It may also be mentioned that 22 per cent were prematurely born (birth weight less than 2,500 g) and 7.5 per cent were twin births.

The patients were classified according to the mental development into normal (40 per cent), mentally retarded but educable (49 per cent) and uneducable (11 per cent). A classification according to the main symptom from the therapeutic view-point gave the following figures: spasticity as the only or predominating symptom, 59 per cent; spasticity and marked extrapyramidal and/or cerebellar symptoms, 18 per cent; no spasticity (athetosis, rigidity, ataxia, atonia or mixed forms), 23 per cent. Among the other prominent symptoms was epilepsy; it was present in 15 per cent of the mentally normal children, in 24 per cent of the mentally retarded and in 38 per cent of the uneducable. Disturbances in the function of the eye muscles were found in 40 per cent of the whole series.

The main form of therapy has consisted of sets of exercises of muscular movements, adapted to the individual case and started as early as possible. Other forms of therapy, e.g. orthopaedic surgery or applicances, speech therapy, and the choice of suitable institutional care or schooling, have also been individualized as far as possible. The cerebral palsied child has consistently been regarded as a whole, and the psychological and humanitarian side of treatment has been considered to be of at least as great importance as more specialized forms of therapy.

Air-encephalographic Findings in Cerebral Palsy

by SIGURD EEK

Radiological Department, Children's Hospital, Rikshospitalet, Oslo

Among 320 patients in a cerebral palsy material, 85 were subjected to an air-encephalographic examination (LEG). Among them were 27 examinations which were discarded as incomplete or unsuccessful. Among the 58 successful examinations there were 10 showing a normal ventricular system. The remaining 48 were definitely pathological. The 10-to-48 ratio of normal to pathological LEG's is presumably not representative for the whole of the material, for it was usually the worst cases which were examined. A selection of encephalograms, representing various clinical types of cerebral palsy (right- and left-sided hemipareses, bilateral spastic pareses, athetosis and mixed forms) is demonstrated. Representative Röntgenograms of cases of pure ataxia are lacking.

The 58 cases showing a successful LEG are classified according to type in the following way:

	Normal LEG	Pathological LEG	Total
Hemiparesis			
Right-sided	1	5	6
Left-sided		3	3
Bilateral spastic paresis	6	19	25
Athetosis	2	2	4
Ataxia		1	1
Mixed form	1	18	19
	10	48	58

Among the 48 patients with a pathological LEG was one with right-sided hemiparesis and signs of local cortical damage as the only finding. All the other 47 patients showed diffuse, central damage—general dilatation of the lateral ventricles, dilatation of the third and/or fourth ventricle and large basal cisterns. The dilatation of the third ventricle was by far the most common finding. Several of the patients also showed at the same time radiological manifestations of cortical damage, either diffuse or, in the case of the hemipareses, local. If a comparison is made of the LEG and EEG findings in the 58 cases with successful LEG, the present material shows better agreement between the air-encephalographic and clinical examinations than between the electro-encephalographic and clinical examinations. Among the above-mentioned 58 patients 39 were subjected

to EEG examinations. It was particularly in the group of bilateral spastic paresis cases that the findings were most at variance; among the 19 patients showing a definitely pathological LEG there were 17 given an EEG examination, and among them were 8 showing normal electro-encephalographic conditions.

Roentgenological Conclusions

1. With only one exception, all the 48 cerebral palsy patients with pathological air-encephalographic findings showed damage to the central cerebral structures irrespective of the clinical type.
2. A particularly common finding is a pathological dilatation of the third ventricle (more than 8 mm wide) indicating damage to the nuclei and/or nerve fibre tracts in the area of the basal ganglia. The radiological evidence cannot decide *which* structures are involved.
3. In 8 of the 9 cases of hemiparesis examined, pathological changes, to some extent considerable, were found on the side corresponding to the clinical lesion. But in 7 of these 8 cases there were other changes of a more general character without any corresponding clinical finding.
4. Cases of bilateral spastic paresis, pure athetosis, pure ataxia or mixed forms present nearly always the same radiological picture. Patients presenting marked spasticity often show considerable dilatation of the fourth ventricle.
5. In some cases congenital malformations such as agenesis corporis callosi, septum pellucidum cysts, etc. were found. In other cases it was, however, not possible to decide on the radiological evidence whether the cause of the pathological findings was a congenital malformation or damage inflicted before, during or after birth. It will therefore often not be possible to decide by radiological means whether a cerebral *atrophy* exists.
6. LEG may be normal in patients with slight clinical symptoms. This is very often the case in the group of bilateral spastic pareses.
7. In the present material the air-encephalographic examinations were superior to the electro-encephalographic examinations with regard to the demonstration of pathological changes in the cerebrum.

Blood

The Osmotic and Mechanical Resistance of the Red Blood Cells of Foetus and Child

by STIG SJÖLIN

The Children's Hospital, the Academic Hospital, Uppsala, Sweden

The osmotic resistance of the red blood cells shows certain characteristic changes during foetal life and childhood. This resistance is considerably lower in the young foetus than in the blood in the umbilical cord of a full-grown infant. On the other hand, this resistance is practically the same in the older foetus as it is in the blood of the umbilical cord. The blood in the umbilical cord and during childhood shows an increase of the number of resistant red cells in comparison with adults. The variations in osmotic resistance can at any rate to some extent depend on a form factor. These variations may be taken to depend on differences in the composition of the red blood cell population or on differences in the red blood cells in an *in vivo* environment. *The mechanical resistance* of the red blood cells is reduced during the first two or three months of life and under different haemolytic morbid conditions (congenital haemolytic anaemia, acquired haemolytic anaemia, erythroblastosis).

The Water- and Ion-Permeability of the Foetal Red Blood Cells

by STIG SJÖLIN

The Children's Hospital, Academic Hospital, Uppsala, Sweden

The red blood cells of the umbilical cord show a lower permeability for water than the red blood cells of adults. The red blood cells of the umbilical cord lose potassium and take up sodium more quickly when stored at a low temperature ($+4^{\circ}\text{C}$) than do the red blood cells of adults. These differences of permeability are interpreted as indicating membrane qualities which vary in the two types of cells.

Investigations of the Blood of the Umbilical Cord

by URBAN FURUHJELM, IRJA SALMI and KALLE ÖSTERLUND

Children's Hospital, Helsingfors, Finland

This investigation concerns analyses of the arterial and venous blood of the umbilical cord and of the venous blood of the mother. The content of

the following substances in the plasma was determined: Calcium, magnesium, potassium, sodium (K and Na also intracellular), proteins, alkali reserve, chlorides (also intracellular) proteins, alkali reserve, chlorides (also intracellular) and non-organic phosphorus. The blood sugar and total fat in the serum was also investigated.

It was found that the Ca content was always higher in the umbilical vein than in the umbilical artery, whereas the K and Na content was evidently the same in arterial and venous blood. The protein figures were somewhat higher in the arterial blood than in the venous blood of the umbilical cord. A "chloride-shift" was observed in the case of Cl. The alkali reserve was remarkably low in the mother, whereas the figures for umbilical cord blood were somewhat higher, although definitely lower than the normal in the new-born. The sugar content of the blood of the umbilical vein was always higher than of the umbilical artery (in some cases the figures were the same), and there was a positive correlation with the figures for the mother. The total fat was sometimes higher in the artery, sometimes in the vein. The means were of the same size, and there was a positive correlation with the mother's blood.

Roentgenological Findings in the Bone System of Leukaemic Children

by PER-ERIK HEIKEL and RUTH WEGELIUS

Children's Clinic, Helsinki, Finland

Changes in the long bones were found in 72 of 93 children suffering from leukaemia. In some of the cases the changes appeared before any pathological findings were observed in the bone marrow and the peripheral blood. The changes consisted mainly of zones of metaphyseal decalcification and periosteal reactions. Osteolysis and osteosclerosis were also found.

Treatment of the Anaemia of Praematurity with Cobalt

by RUTH WEGELIUS

Childrens Ward, Maria Hospital, Helsingfors, Finland

0.30 mg cobalt was given daily i.m. during a 10-day period to premature babies suffering from anaemia. An increase of the reticulocyte count, the haemoglobin value and the erythrocyte count were observed during the

treatment. 5 mg cobalt chloride given per os every other day after the intramuscular treatment did not cause any further increase of the Hb and the red blood cells.

Exchange Transfusion in the Haemolytic Disease of the Newborn

by H. R. NEVANLINNA

Children's Clinic, University, Helsinki, Finland

The technique and results of exchange transfusion in 120 cases of haemolytic disease of the newborn due to maternal Rh immunization with a mortality rate less than 10 per cent are presented.

Anaemia in Childhood

RUTH WEGELIUS and MARJATTA KUNNAS

Children's Clinic, Helsinki, Finland

306 children with anaemia were admitted to the hospital during 1 year. The number of children aged 0-1 year exceeded the number of anaemic children aged 2-15 years. About 65 per cent of the anaemic children under 2 years suffered simultaneously from acute respiratory infections.

Anaemia Hypoplastica Congenita (Anaemia Typus Josephs-Diamond-Blackfan)

Report of a successfully Treated Case with Adrenocorticotropic and Cortisone

by ARNE KASS and ALFRED SUNDAL

Children's Clinic, Univ. Clinic, Bergen, Norway

A case of anaemia of the Josephs-Diamond-Blackfan type in a 6 year old girl is described. The clinical features were typical, with a marked reticulocytopenia as the most striking haematological finding. She has been dependent on regular blood transfusions with short intervals, most frequently of 4-6 weeks, until the therapy mentioned here was started. After two courses with ACTH treatment there was a marked increase in the reticulocyte count which occurred both times on the 9th day after starting the treatment. It lasted several weeks, accompanied by a spontaneous remission of the blood values. Thus the intervals between the transfusions

have been prolonged for 15 weeks. A third course with ACTH gave the same response and the treatment was continued with Depot-ACTH (long-acting ACTH) twice a week for about 8 months. The next blood transfusion was necessary after $9\frac{1}{2}$ months.

As the patient had been given no treatment for about $2\frac{1}{2}$ months, she had a marked anaemia. In March 1953 peroral cortisone therapy was then started and was followed by a spontaneous rise in blood values up to the normal. The therapy has later been given permanently in variable doses; the minimal dose needed seems to be 5 mg pro die.

18 months have elapsed since the last blood transfusion. The patient is in excellent condition.

The blood values, doses of the drugs, etc. were shown in figures.

Three Cases of Agammaglobulinaemia

by NILS KULNEFF

Central Hospital, Halmstad, Sweden

Infant Mortality

The Infant and Early Mortality in Gothenburg

by YNGVE ÅKERRÉN

Children's Hospital, Gothenburg, Sweden

Continued report (cf. Lecture at the Congress in Helsingfors and Exhibition at the Congress in Stockholm) of the infant and early mortality during the years 1951–53 and a comparison with earlier figures.

Year	Living births No.	Deaths during first year		Deaths during first week		Still-births	
		No.	%	No.	%	No.	%
1941–45	27,154	750	2.76	445	1.64	569	2.05
1946–50	30,947	608	1.96	412	1.33	521	1.66
1951	5,559	107 ¹	1.92	77 ¹	1.39	79	1.40
1952	5,464	103 ¹	1.89	76 ¹	1.39	114	2.04
1953	5,615	63 ¹	1.12	45 ¹	0.80	93	1.66
1951–53	16,638	273 ¹	1.64	198 ¹	1.19	286	1.69

¹ The figures for these years are preliminary.

Infant Mortality in Finland

by HILKKA TÄHKÄ and NIILU HALLMAN

Children's Clinic, Helsinki, Finland

The changes in infant mortality in Finland are shown, pointing out the increased mortality during and shortly after the war and the rapid decrease in the death-rate in the last few years. The infant mortality is at present nearly 3 per cent (in the year 1940, 8.7 per cent). This decrease has been caused mainly by the reduction of all infectious diseases. Infantile diarrhea which has been one of the most important causes of death until recent years, is now practically wiped out. The mortality during the first week of life has not kept pace with the falling infant mortality.

Pneumonia and Hyaline Membranes in Newborn Infants: An Autopsy Material

by K. H. TORP and KR. HARNÆS

*Pediatric Department and the Institute of Pathological Anatomy, University of Oslo,
Oslo, Norway*

The authors have examined 169 stillborn infants and 253 infants who died in the neonatal period. The results are published in the Archives of Disease in Childhood.

Child Psychiatry

One of Identical Twins Presenting Manifest Reading Difficulties

by KARL-HENRIK KARLÉN

*Child Psychiatric Department, Kronprinsessan Lovisa's Children's Hospital,
Stockholm, Sweden*

Tests for Children with Special Difficulties in Reading and Writing

by SVEN AHNSJÖ

School Hygiene Department of the Royal Board of Education, Stockholm, Sweden

The exhibition of tests for reading and writing is a result of an investigation that has been conducted to try to find a simple reading and writing

test as much as possible adapted to its purpose for children with special reading and writing difficulties. It should also be a compensation for all non-standardized tests, which have been used during the 1940's in Sweden and it should also be a compensation for other more incomplete series of tests.

Earlier tests have been given a trial in special (reading) and normal classes in Stockholm during the school years 1948-49 and 1949-50 on 350 children for individual tests and maximum 615 children for group tests in the reading classes 2-5, and on 205 and 322 children, respectively, in the corresponding normal classes 2-5. On the basis of these tests, which have not shown a considerable difference between the two classes, we have been able to form an opinion about their value for estimating the reading and writing difficulties, above all the degree and also in some way the kind of difficulties.

For the tests children have been selected in reading and normal classes from different parts of Stockholm. The results concern the years 1948/50 in the elementary schools of Stockholm. In the other parts of the country such a test cannot be carried out because the system with reading classes has not been developed in the same way there. At this time we thought that in Stockholm we had reached from a pedagogical point of view, a suitable arrangement regarding the clientele in the reading classes and that the admitted frequency of children in these classes would not grow too much in the future. An analysis of these circumstances has now shown that the number of children in reading classes 2-5 during the years 1948-49 to 1952-53 has indeed increased from 482 to 867 but also that this addition on the whole is due to the increase in the number of children and not to a change in the proportion between the number of children in the special and normal classes during these years.

In addition to the above-mentioned tests contemporaneous trial has been made of a test consisting of "mutilated words" and another one with "mutilated pictures", taken from L. L. Thurstone's Gestaltpsychological test series.

This investigation has shown that several of the tests used can be discarded owing to their low differentiating capacity between the children in reading and normal classes.

The tests for reading and writing comprise, class to class, five to six tests for the classes 2-5. The result of the different tests has been given with solution frequencies and averages for reading and normal classes.

Some of the results of the tests with Thurstone's word and picture test complete the series.

The word test with "mutilated words" has proved to be very useful and it is suggested as a suitable basic group-test for teachers when it is a question of selection for ordinary medical psychological examinations. As a support test the picture test with mutilated pictures can be used. The results in the reading classes were approximately the same as in normal classes. The picture test thus shows that the children in reading classes are not handicapped when it is a question of "Gestaltformation" on the visual picture area. This result corresponds well to what we usually find with children with special reading and writing difficulties at intelligence tests according to Terman Merrill where the discrepancy between visual and auditory learning and memory functions can usually be seen very clearly, for example when Terman Merill's profile schedule is used. The maximal results produced in the area of observation are here often higher than the maximal results produced in the acoustic sphere.

The advantages of the exhibited reading and writing test compared with other similar tests lie, among other things, in the comparison between the tested clients' result and the average result in both normal and special classes, for which reason the degree of the tested difficulties can be easier judged.

This like other similar tests is of course meant to come after it is made clear in the usual way that reading and writing difficulties are not secondary to e.g. general mental retardation, visual or hearing defects or similar ailments.

Skeleton

Some Results of Operative Treatment for Craniosynostosis

by L. LAITINEN and M. SULAMAA

Children's Clinic, Helsinki, Finland

When a cranial suture obliterates prematurely, the growth of the large bones of the skull ceases perpendicular to the fused suture and skull deformities occur. When the sagittal suture fuses the skull remains narrow and antero-posterior expansion occurs as a compensatory development, and the typical dolichocephalic or scaphocephalic deformity appears. When the coronal sutures fuse prematurely, the antero-posterior growth from the obliterated sutures ceases. There is a compensatory lateral and vertical expansion of the skull so that brachycephalic deformity or tower skull appears.

The most usual of these synostosis types is the one affecting the sagittal suture. Depending upon the obliteration of one or more sutures together, different types of skull deformities appear.

There are often with this disease other anomalies also, of which syndactylies, very often symmetrical, are the most common.

Sometimes the compensatory growth of the skull is not enough for the brain growth and there will arise—because of the increased intracranial pressure—different symptoms, headache, sometimes convulsions and later visual disturbances, papilledema and optic atrophy, which may lead to total amaurosis. There are often exophthalmos and strabismus which are due to orbital deformities.

The increased intracranial pressure which can be found easily by lumbar puncture may be a factor causing the communicating hydrocephalus, which is common among these patients.

The intelligence of the patients is usually normal. In severe cases there can be mental retardation.

The treatment is operative. Because the weight of the brain has doubled during the 7 first months of life, and has become almost full grown during the three years of life, the operation should be performed as early as the first few months of life.

The general plan of treatment is to perform a linear craniectomy in the region of the fused suture. The margins of this opening are covered with polyethylene film to prevent or retard the rapid regeneration of the bone. The operation is performed under local anaesthesia and it is rather easy to perform.

There has been no operative mortality among the about 150 operations performed in the U.S.A. and in Finland.

The results of the operative treatment have been excellent, when the patient has been treated during the first year of life. The cosmetic results have also been good in patients treated early in life.

At the University Children's Clinic in Helsinki 23 craniosynostosis patients have been treated during 1949–1954 with linear craniectomy ad m. Ingraham. From these 8 cases representing different deformities of the skull have been chosen for the Exposition of the Northern Paediatric Congress in Oslo 1954. The photos and X-ray pictures show the results of the operation. There is also one which has not been operated on.

Chondrodystrophia Calcificans Congenita Punctata ("Stippled Epiphyses")

by ARNE KÄSS

Children's Hospital, University Clinic, Bergen, Norway

This condition was first described by CONRADI (1914). Later about 40 cases have been reported.

There is a mild type of the condition in which the discrete centres of calcification in cartilaginous epiphyses are the only symptom and disappear during the first years of life without leaving any skeletal abnormalities.

The severe type of the condition forms a syndrome consisting of achondroplasia and "stippled epiphyses" together with cataracts and mental deficiency. In these patients pronounced limitation of movement in the joints may be found—giving a clinical picture similar to arthrogryposis multiplex.

At the exhibition three cases were reported.

The first case was a mild type with the stippling of the epiphyses as the only symptom.

The second and third cases were sibs—the only children of young, healthy parents without consanguinity. The mother was well during her pregnancies and she gave birth to her infants with a 17 months interval.

At admission to the hospital, 7 and 6 weeks old, both of the babies showed a completely similar appearance: short, achondroplastic limbs with flexion deformities and cataracts. The radiographs showed stippling of the epiphyses in numerous bones. The first baby was observed in the hospital for about six weeks and died at home 6 months old. The second infant, who also had symptoms of vitium cordis congenitum, was observed until death in hospital at the age of $3\frac{1}{2}$ months. Both of them showed during the observation time a distinct mental retardation.

Serum chemistry gave normal levels of serum calcium, phosphorus and alkaline phosphatase.

Courses of treatment with ACTH and cortisone were not followed by any change in the clinical nor the radiographic pictures.

At the exhibition the case histories were reported and photographs and X-ray pictures of the patients were shown. Pictures of the histological post-mortem findings of the third patient were shown, demonstrating the abnormal picture of the cartilage and the irregularity of the ossification line.

Infantile Cortical Hyperostosis. Development of a Case in Utero

by SIGURD EEK

Radiological Department, Children's Hospital, Rikshospitalet, Oslo

Typical Röntgenograms of a case of infantile cortical hyperostosis of intra-uterine origin are demonstrated, showing considerable periosteal thickening of several bones, most marked in the long canalised bones. These also show to some extent a considerable increase in longitudinal growth—a phenomenon which does not seem to have been described earlier, and which challenges the theory, in vogue at the present time, assuming that this disease depends on tissue anoxia.

Miscellaneous

Accidents to Children in Sweden

by N. BEJEROT and R. BERFENSTAM

Pediatric Clinic, University Hospital, Uppsala, Sweden

Accidents to children are among the most urgent problems of preventive child care. In Sweden death by violence accounts for more deaths than any disease. At certain ages as many children die of accidents as of all the diseases put together.

Pre-school children are hardest hit; especially between two and four years of age children are exposed to great dangers. The material dealing with death by accidents shows that boys clearly predominate. This appears already during the first year of life but becomes more and more pronounced as age increases: in the 10–15 years age group six times as many boys as girls die of accidents.

Drowning accounts for $\frac{1}{3}$ of all deaths, traffic accidents for $\frac{1}{4}$. Among accidents in the home various types of suffocation claim about 30 victims a year, burns the same number and poisoning about ten.

For many years organisations and individuals in Sweden have fought for the prevention of accidents, mainly traffic accidents and drowning. But accidents in the home and other types of accidents occurring in the pre-school stage demand an especially intensive campaign for prevention; in these cases propaganda must go via the home.

A motion in the Swedish Parliament supported increased aid to research and propaganda against accidents in childhood.

Studies of the Respiration and Circulation during the Neonatal Period

by G. BERGLUND, P. KARLBERG and J. LIND

Pediatric Clinic, Karolinska Sjukhuset, Stockholm, Sweden

1) A survey of the normal ventilation (ventilation of the lungs + the gas exchange between the alveolar air and the pulmonary capillary blood) is given. The different static lung volumes with their subdivisions and the different dynamic ventilatory divisions are defined. A schematic diagram shows the respiratory mechanism in a single normal breath. The respiratory function tests, at this time in newborns, are given. The definitions and symbols of respiratory physiology, proposed by the American Standardization Committee (J. R. PAPPENHEIMER *et al.*, *Federation Proc.*, 9: 602, 1950) are introduced.

2) Studies of ventilation and gas exchange during the newborn period are presented (performed at the Boston Lying-in Hospital, Boston, together with C. D. COOK, D. O'BRIEN, R. B. CHERRY and C. A. SMITH). Figures for minute volume, respiratory rate, tidal volume, alveolar ventilation, functional dead space and the energy required for the work of respiration are given for normal newborns and babies in "respiratory distress". (Since the exhibition, this part of the work has been published in *Acta Paediat.*, Suppl. 100: 397, 1954.)

3) Determination of the functional residual capacity in newborns. A method is described and preliminary results given, showing that the functional residual capacity during the newborn period is about one-third of that of an adult, when compared to individual body size. Newborns in "respiratory distress" are found to have a much smaller capacity.

4) Hypothermic treatment in cases of "respiratory distress" is outlined. Two cases with severe pulmonary atelectasis treated in this way are reported. In one of these cases an angiographic study was performed. When the clinical symptoms were most pronounced, a shunt from the right to the left auricle was seen. One month later angiography showed normal circulation.

5) Circulatory studies during the newborn period (together with C. WEGELIUS). Schematic diagrams of the fetal circulation and of the different steps during the transformation of the fetal circulation into an adult type circulation are given. Angiographic studies showing the closure of ductus venosus, ductus arteriosus, foramen ovale and the haemodynamics during the newborn period are presented. The transformation of fetal to adult cir-

culation passes through an intermediate state, the neonatal circulatory type, characterized primarily by the functional closures of the fetal circulatory channels, the patency of which can be renewed under adverse conditions. This is shown by angiographic studies in pathologic cases. The change-over of the circulation is intimately associated with the establishment of pulmonary respiration.

Working Capacity in Relation to Age, Sex and Body Weight

by ELIAS BENGTSSON

Infectious Diseases Hospital, Stockholm, Sweden

The heart rate increases linearly with the intensity of exercise up to a rate of about 160 beats per minute.

The linear relationship shows a varying deviation in different age groups; it deviates earlier in pre-school children, and somewhat later in older children and adult males. The higher the working capacity, the further the linear relationship reaches.

The maximum working capacity seems to be reached at an average of about 200 beats per minute in untrained individuals between the ages of five and forty. The relationship of heart rate and exercise at rates of up to 160–170 beats per minute indicates the velocity with which the circulatory adaptation approaches, via increasing heart rate, its maximum for adequate circulation.

The exercise performed at any given heart rate can be used as a measure of the velocity with which the heart rate increases with increasing amounts of exercise.

This exercise can be shown in relation to age, body weight, sex, etc.

The working capacity increases linearly with mounting age from the age of five throughout childhood up to the age of twenty. Between the ages of 21 and 40 it is fairly constant, though the individual variations are greater than in children.

The body weight shows major variations in different age groups, and the individual variations will be smaller if the series is grouped according to body weight instead of age, at all events in childhood.

The correlation between body weight and exercise intensity is greater in children than in adults.

In children the correlation between body weight and exercise intensity is $r = 0.85-0.90$ even at such a relatively low heart rate as 130, but in adults this is not the case until a heart rate of 160–170 beats per minute has been

reached. The higher the exercise intensity and the heart rate under steady conditions, the smaller will be the individual variations.

In calculating the working capacity we should take into account notably the age and body weight, but also certain other factors such as degree of training, constitution, balance in the vegetative nervous system, and psychic state.

The sex factor influences the working capacity only in persons over the age of fourteen.

The respiration rate, like the heart rate, shows a linear increase with mounting exercise intensity. Here, however, the linear relationship is less pronounced, at all events in children.

Deviation of this linear relationship varies with age, being earliest in adults and in the oldest children (at about 32 respirations per minute), then later as the age decreases; and in the youngest children—the five or six year olds—the relationship still appears to be linear at 50 respirations per minute. The frequency of respiration is also affected by other factors, however, especially in children. Indeed, the effect here is so marked that calculation of the working capacity by means of this relationship is inadequate, though it may well implement other examinations, for instance in the differential diagnosis of conditions affecting the alveolar diffusion and the pulmonary circulation.

The respiratory minute volume increases linearly with exercise intensity, and the same applies to the oxygen consumption and the amount of carbon dioxide expired. This increase in the oxygen consumption is not dependent on age or body weight, and appears to have the same relationship to the exercise intensity as that earlier described in adults. The net mechanical effect seems to be equal in children and adults.

Since the minute volume of the heart increases linearly with the amount of exercise, and the stroke volume is proportional to the amount of exercise at any given heart rate, it is the maximal stroke volume that is studied under steady conditions in determinations of the heart rate during exercise tests. This stroke volume is dependent, among other things, on the state of the valves and on the contractility of the myocardium. Hence the functional capacity of the heart in myocardial insufficiency and valvular disease can be examined by taking the pulse during bicycle ergometer tests, provided these are carried out with graduated amounts of exercise, over an adequate length of time, and under steady conditions.

Epidermolysis Bullosa Hereditaria Dystrophica

A Genealogical Investigation

by H. ENELL and M. PEHRSON, Boden, and B. HALLGREN, Stockholm

Pediatric Dept., Military Hosp., Boden, Sweden

Epidermolysis bullosa is a rare, hereditary, well-defined disease, which appears in three main forms of varying severity. The milder forms are genetically dominant and the most serious recessive. Concerning the intermediate forms, the so-called dystrophic types, which do, however, cause a significant degree of invalidity, there are divergent points of view as to the mode of inheritance, and genetic analyses seem to confirm that both types of heredity occur.

Taking the case of a patient treated at the Pediatric Department, Garnisonssjukhuset, Boden, the demonstrators have tried to make as complete a genealogical analysis of the relatives as possible. The genealogy of 747 persons was studied and 6 secondary cases of epidermolysis bullosa hereditaria dystrophica were discovered. Altogether the material consists of 7 cases belonging to 6 families. In 5 of these families the parents were related and it was in these cases possible to chart the probable heterozygote lines. Since the group has lived in an isolated region, it has in certain cases been possible to trace back the ancestry for eight generations. Intermarriage within the family has occurred frequently. Of the affected persons 3 were boys and 4 girls, while the healthy siblings included 12 boys and 7 girls. The material is insufficient for Mendelian analysis. In this particular group heredity undoubtedly points to a monohybrid recessive inheritance.

The demonstration material consists of a pedigree chart as well as short case histories, clinical data and some photographs of the affected children.

Vitamin D Intoxication

by BJARNE ANDERSEN

Pediatric Department, Ullevål Hospital, Oslo, Norway

(Publ. in "Tidsskrift for Den Norske Lægeforening" 12: 1954, 419)

Four cases of intoxication with Vitamin D (Calciferol) are reported. The children were 16 months to 5 years old. No. 1 and No. 2 received large doses within a short time (10 million U. in 6 weeks and 3 mill. U. in 2 weeks). Both recovered rapidly when Calciferol was discontinued. No. 3

and No. 4 got smaller daily doses, but treatment was continued over a very long period (25 mill. U. in 1 year and $12\frac{1}{2}$ mill. U. in $\frac{1}{2}$ year). After discontinuing the vitamin for 17 weeks in cases 3 and 4, the children still had their symptoms nearly unchanged.

All the patients had gastric and renal impairment signs, hypercalcaemia and increased blood-urea.

Three had band-keratitis (Nos. 2, 3 and 4). Two (Nos. 3 and 4) had changes in the roentgenograms of the long bones.

Radiological Findings in Cases of Infantile Hypertrophic Stenosis of the Pylorus

by SIGURD EEK

Radiological Department, Children's Hospital, Rikshospitalet, Oslo, Norway

In the overwhelming majority of cases infantile hypertrophic stenosis of the pylorus involves only the canalis part of the stomach. The duodenal bulb, with its duodenal pyloric part, is not involved, and patient No. 1 is a fair sample. This condition ought therefore to be called infantile hypertrophic canalic stenosis.

The whole of the canalis part of the stomach is hypertrophied, and the stenosis is usually of a stereotyped thread-like character undergoing little variation. It is quite exceptional to find peristaltic waves in the beginning of the canalis as in patient No. 2. In a long series of cases more or less prolapse of the gastric mucosa had reached the duodenal bulb so as to give it the shape of a parachute as in patients Nos. 3 and 4. This prolapse disappears on recession of the stenosis. It is not rare to find ulcers of the mucosa in the juxta-pyloric part of the canalis as the result, in all probability, of trophic disturbances. Patient No. 4 is an example of this condition. These ulcers disappear soon after the stenosis has been corrected.

Technique.—Through a naso-gastric tube some 15 ml of a barium contrast are introduced into an empty stomach. Thereupon the patient is examined as soon as possible in an upright position, hanging in a bag, before the contrast fills the pars ascendens and covers the canalis area. In cases of retention the patient is also examined after 3 and 24 hours.

Placental Dysfunction in Postmaturity

by PER SELANDER

Flensburg's Children's Clinic, Malmö, Sweden

Of 1,330 children examined at the Women's Clinic in Malmö 12.0 per cent exhibited dry, macerated, wrinkled skin, especially on the palms of the hands and the soles of the feet, brown pigmentation of the nails and the umbilical cord, intense erythema of the external genitals and desiccation ("Ballantyne-Runge's syndrome"). Of the children who were born more than 4 days after the calculated date 20.3 per cent had the syndrome, whereas of those who were born less than 4 days before the calculated date 3.2 per cent displayed the syndrome. Of the 160 children with the syndrome 58.8 per cent were postmature by more than 4 days. Of those with a pronounced syndrome 73.0 per cent were postmature more than 4 days.

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IMPLICATIONS OF AGENESIS OF THE SPLEEN ON THE PATHOGENESIS OF CONO-TRUNCUS ANOMALIES IN CHILDHOOD

An Analysis of the Heart Malformations in the Splenic
Agenesis Syndrome, with Fourteen New Cases

By

BIÖRN I. IVEMARK

Almqvist & Wiksell's Boktryckeri AB UPPSALA

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FROM THE DEPARTMENT OF PATHOLOGY, CHILDREN'S HOSPITAL, BOSTON
(CHIEF: PROFESSOR SIDNEY FARBER); THE DEPARTMENT OF PATHO-ANATOMY,
KAROLINSKA INSTITUTET, STOCKHOLM (CHIEF: PROFESSOR ÅKE WILTON),
AND THE PEDIATRIC CLINIC, KAROLINSKA SJUKHUSET, STOCKHOLM
(CHIEF: PROFESSOR ARVID WALLGREN).

IMPLICATIONS OF AGENESIS OF THE SPLEEN ON THE PATHOGENESIS OF CONO-TRUNCUS ANOMALIES IN CHILDHOOD

An Analysis of the Heart Malformations in the Splenic
Agenesis Syndrome, with Fourteen New Cases

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Printed in Sweden
Ivar Haggströms Boktryckeri AB
Stockholm 1955

To my Father and Mother

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Preface

This study was begun and the major part of it was carried out in 1953 at the Department of Pathology, Children's Hospital, Boston. The chief of that department, Professor Sidney Farber, and his staff showed a continuous and stimulating interest in my work. Professor Farber gave me generous permission to include in this study all the cases of absence of the spleen and certain other cases of splenic malformations from that department. Professor Farber and Doctor Betty B. Geren have given helpful and detailed criticism of the manuscript.

The final stages of my work, the taking of the photomicrographs and the compilation of all data have been completed at the Department of Patho-Anatomy, Karolinska Sjukhuset, Stockholm. The chief of that department, Professor Åke Wilton, has put all the facilities of his institution at my disposal and has besides given valuable criticism of my manuscript. Professor Wilton, and Docent Bengt O. Engfeldt and Docent Kaj H. R. Lindberg of his staff have shown great interest in my study and have never failed to encourage its completion.

Professor Gösta Häggqvist, chief of the Department of Histology, Karolinska Institutet has generously offered for my study all the embryos described. Professor Häggqvist has also checked the slides for presence of splenic primordia and has given many valuable suggestions concerning their description and relative age. Docent Lars Gyllensten of his staff has critically reviewed the sections on embryology.

Professor Nils Ringertz, chief of the Department of General Pathology, Karolinska Institutet, and my former chief, has closely followed this study from its initiation to its completion. By personal guidance and constant stimulation he has helped me through the final stages of the study. In addition, Professor Ringertz has given me permission to include Case 1.

The chiefs of the two Pediatric Clinics at Karolinska Institutet, Professors Curt Gyllenswärd and Arvid Wallgren, have shown interest in my work and great understanding of the time-consuming final stages of this study.

Docent Sven Roland Kjellberg and Docent Lars A. Werkö have made valuable suggestions and constructively criticized the manuscript. Docent Gunnar Ekström has generously discussed the clinical and surgical view-

points. Doctors Håkan Arvidsson, Erik Berglund, Docent Rolf Zetterström and Doctor Thor Alm have all given valuable suggestions during long discussions.

The statistical calculations have been made by Thøger Busk, Ph.D., the Department of Statistics, University of Copenhagen.

Doctor Daniel Stowens, Armed Forces Institute of Pathology, Washington, D.C., has given me permission to include Case 7.

The gross photographs were taken by Mr. Ferdinand R. Harding and his assistants at the Children's Hospital, Boston.

Mrs. Astrid Binett has given efficient secretarial aid.

Miss Ruth B. Cherry, M.A., has gone over the manuscript from the language point of view.

To all the above I extend my warmest thanks.

My wife, Barbro, has given technical assistance in serially sectioning many embryos in the search for early splenic primordia, and she has shown inexhaustible patience throughout the work. To her I give my heartfelt thanks.

I am greatly indebted to the Rockefeller Foundation for the fellowship which made possible the year of study at the Children's Hospital, Boston.

Finally, I express my gratitude to the printers at Ivar Hæggströms Boktryckeri AB for their helpful cooperation.

Stockholm, October 1955.

Biörn I. Ivemark

Introduction

Until recently, little attention has been paid to malformations of the atrio-ventricular region in cases with anomalies of the cono-truncus. Malformations of the latter have usually been studied separately and by comparisons among cases displaying various anomalies of the cono-truncus. With the exception of tricuspid and mitral atresia, malformations of the atrio-ventricular valves have usually not been studied in association with malformations of the cono-truncus.

Recently, *Shaner* (1949) pointed out the frequent occurrence of malformations of the atrio-ventricular canal cushions in cases of congenital malformations of the heart in pig embryos. This author carried out micro-dissection on 20,000 embryo pigs (1951). By this approach *Shaner* caught the anomalous heart in an earlier stage of malformation than had been achieved before. *Shaner* found 48 embryos with malformed hearts. A large percentage of these had anomalies of the cono-truncus associated with malformed atrio-ventricular canal cushions. *Shaner* considered the former to be caused by the latter.

That this also might be the case in human hearts with anomalies of the cono-truncus has been emphasized by *Doerr* (1952, a and b). That author stresses the frequent association of atrio-ventricular anomalies and congenital pulmonary or aortic stenosis.

This paper deals with the problem of whether there is any relationship between anomalies of the two mentioned regions in the heart. Cases of cardiac malformations associated with agenesis of the spleen will be analyzed. By this method of selection, not applied to cardiac malformations before, far-reaching conclusions can be drawn concerning the pathogenesis of certain types of malformations of the cono-truncus region. This is due to the fact that during embryogenesis the spleen is being formed while the heart is still in a stage of critical modeling. By selecting cases of cardiac malformations associated with absence of the spleen, it is postulated that cases are collected in which the basic lesion of the heart during organogenesis occurred while the spleen should have been in its early formative stage of development. Thus, the uniformity of the material is based upon selecting the period when organogenesis of the heart went astray, rather than on similarities in morphology of the malformed hearts.

Congenital heart disease associated with absence of the spleen is usually combined with varying degrees of situs inversus (*Putschar*, 1934). During the 19th century, situs inversus associated with malformations of the heart was studied extensively by pathologists (for references, see *de F. Bauer*, 1944). Among the 20th century cardiologists, "levocardia with subdiaphragmatic lateral heterotaxy" likewise attracts considerable attention (*Forgacs*, 1947; *Robinson & Garfinkle*, 1950; *Thomson*, 1950; *Young & Griswold*, 1951; *Campbell & Forgacs*, 1953).

Malformations of the heart and great vessels in situs inversus are complex, and the anatomic variation from case to case is considerable. Cases lacking a spleen within this group, however, may seem fairly uniform in their anatomic pattern; hence, such cases have recently been considered as constituting a "syndrome" (*Polhemus & Schafer*, 1952; *Gasser & Willi*, 1952; *Boggs & Reed*, 1953; *Baumann*, 1954; *Ivemark*, 1955; *Willi & Gasser*, 1955).

This paper contains four main parts. In the first, the embryology of the cono-truncus and the atrio-ventricular canal at the time of early splenic organogenesis will be reviewed. The author's own contribution in this part includes brief descriptions of the splenic primordia of six human embryos. These embryos have been dated in correspondence with the age groups of *Streeter*. The synchronous developmental levels of other pertinent organs are mentioned. The syndromic nature of embryology is applied. The role of hemodynamic forces in the septation of the cono-truncus is emphasized.

In the second part, the pathology of the splenic agenesis syndrome is described, and 14 new cases with autopsy are reported. It is maintained that the cases constitute examples of a "teratologic syndrome".

The third part deals briefly with cases of congenital heart disease associated with hypoplasia of the spleen and similar cases with multiple spleens.

In the fourth part, the pathogenesis of malformations of the cono-truncus in relation to those of the atrio-ventricular region is discussed. The facts presented are in favor of the concept that atrio-ventricular anomalies may be primary to certain malformations of the cono-truncus.

PART I

Temporal Relations between Splenic Formation, Cono-Truncus Development, and Division of the A-V Canal

For descriptive purposes, embryology can be studied in two different ways. Most commonly, each organ system is traced separately from its early primordia throughout embryonic life. By this method the successive changes in that organ system may be followed closely, and the evolution of a given system is made comprehensible. In the other method, all organs are studied together in age groups in a parallel fashion so as to encompass the interrelations of all organs in embryogenesis. By the latter method, emphasis is placed on the dependence of one organ upon another in morphogenesis. The first-mentioned approach is commonly used for didactic purposes in textbooks of embryology. The second method may reveal interesting interrelations in the morphogenesis of various organs.

The first attempt at systematizing early human embryos into stages of development, or age groups, was made by *Mall* in 1914. Material from the literature and from the Carnegie Embryological Collection in Baltimore was used. Greatest length (G.L.) and external appearance constituted the criteria for grouping. *Mall* found, however, that the material was too scarce to fulfill this plan. Not until 1942 was the project of *Mall* continued by *Streeter* in his paper, "Developmental Horizons in Human Embryos". In the intervening twenty-eight years, the Carnegie Collection had acquired many embryos. In addition, valuable data had accumulated on the timing of rhesus embryos, forming reliable information about the age of primate embryos.

On the assumption that organogenesis is interrelated, *Streeter* based his age grouping on the appearance of certain characters the combination of which constituted a "horizon". The term horizon was chosen by *Streeter* in analogy with archaeology and geology to emphasize "the embryo as a living organism which in its time takes on many guises, always progressing from the smaller and simpler to the larger and more complex" (*Streeter*, 1942, p. 214).

Since very early human embryos were very few in 1942, *Streeter* started with Horizon XI, "13 to 20 somites present", and reserved the designations

I—X for the earlier stages of development, planned so as to encompass the "One-celled egg" (Horizon I) through "Early somites present" (Horizon X).

In 1948, after having covered eight horizons (XI—XVIII), Streeter had confirmed the original idea of embryogenesis' being characterized by a definite and invariable schedule of organ correlation. At any horizon there was a syndrome of features characteristic for that level of development, and the presence of any one of these characters in an embryo indicated the presence of the others.

The definitions of the various horizons consist of scoring points, well defined and easily recognizable on the slides. The age of the embryos was calculated by comparison with macaque embryos of known ovulation age.

Unfortunately, Streeter in his horizons never mentions the appearance of the spleen. This organ does not constitute a scoring point for the characterization of any horizon.

A. The Author's own Investigations on the Early Appearance of the Spleen

As the splenic primordia are not mentioned in *Streeter's* papers, the author has undertaken to study the early appearance of the spleen in relation to the age groups of *Streeter*. Thus, six embryos (Collection of the Department of Histology, Karolinska Institutet) were studied, measuring 9—12 mms. in greatest length (G.L.). All embryos except one had been fixed in formalin; the remaining one, in Carnoy's fluid. They were all well preserved and serially sectioned. They are listed in Table 1. These six embryos showed evidence of splenic primordia in the left aspect of the dorsal mesogastrium.

TABLE 1. Serially sectioned embryos showing splenic primordia

Embryo	G.L.	Sectioning	Section thickness	Fixation	Horizon	Figs.
A	9 mms.	Transversely	10 microns	Carnoy	XV	1—3
Ser. 24	9 mms.	Transversely	10 microns	Formalin	XV	4—6
Ser. 31	9 mms.	Transversely	10 microns	Formalin	XVI	7—8
No. 20	9 mms.	Transversely	10 microns	Formalin	XVI	9—10
Ser. 10	11 mms.	Sagittally	5 microns	Formalin	XVII	11—13
Ser. 32	12 mms.	Transversely	10 microns	Formalin	XVI	14—16

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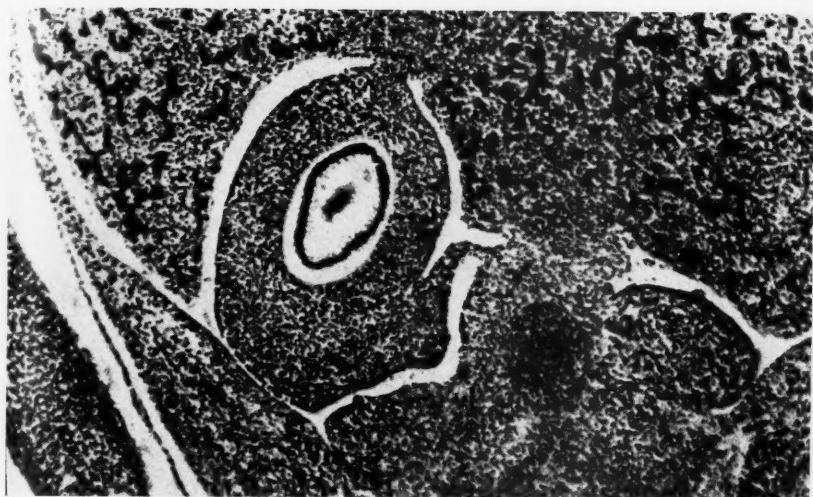


Fig. 1. Embryo A, 9 mms. In the left aspect of the dorsal mesogastrium an area of undifferentiated mesenchymal swelling is seen. This is the area of the future spleen. x38.

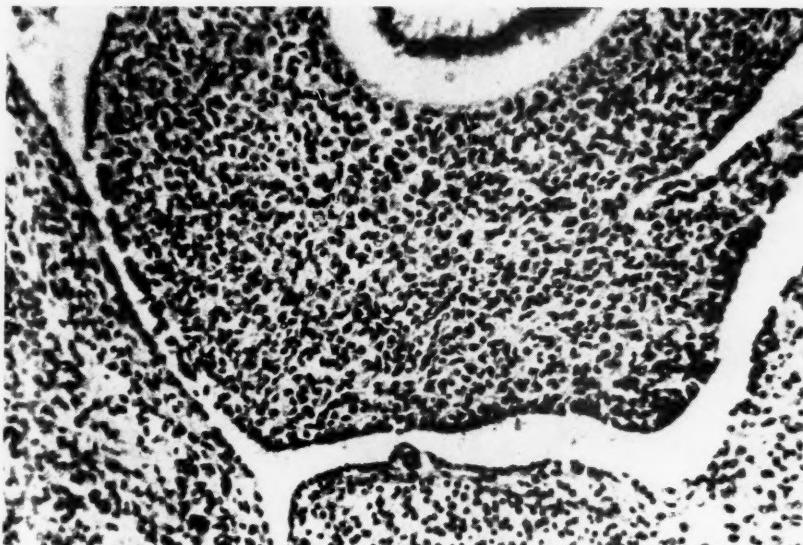


Fig. 2. Embryo A, 9 mms. The dorsal mesogastrium in higher magnification. There is no cytologic differentiation in the mesenchyme. Note the similarity in structure between the stomach wall and the future spleen. No angiogenesis is seen. x136.



Fig. 3. Embryo A, 9 mms. The lens vesicle of the eye is closed. x38.



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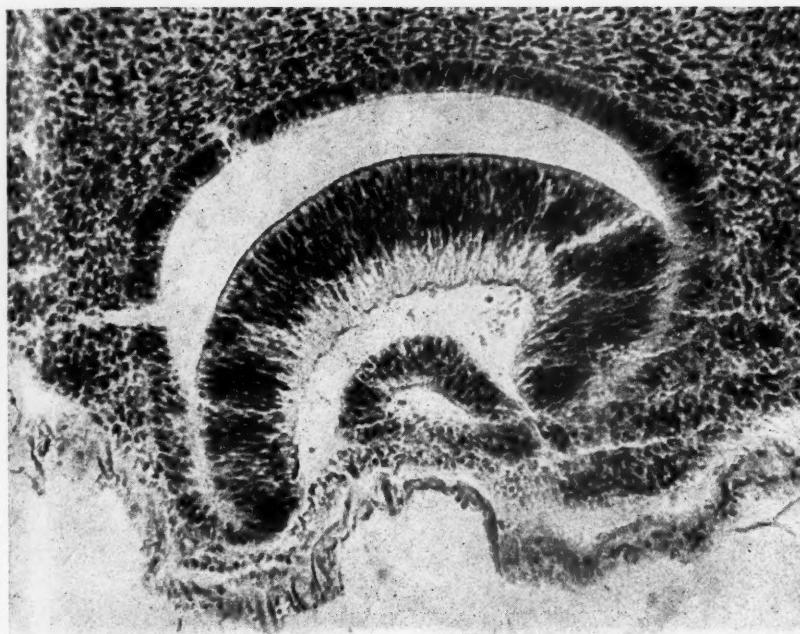


Fig. 5. Embryo Ser. 24, 9 mms. The lens vesicle of the eye is closed. x38.

Embryo A, 9 mms. (Collection of the Department of Histology, Karolinska Institutet), was serially sectioned transversely after fixation in Carnoy's fluid. The sections are 10 microns thick and stained with hematoxylin-eosin. The embryo is in excellent preservation.

The dorsal mesogastrium was thickened and showed an area of bulging to the left (Fig. 1). It was clearly separated from the dorsal wall of the stomach by a recess. The thickened dorsal mesogastrium had the appearance of undifferentiated mesenchyme. Cytologically, this area was indistinguishable from the stomach wall (Fig. 2). There was no evidence of angiogenesis. In view of the thickening, this area was interpreted to be early splenic primordia. Morphologically, this splenic *anlage* was the least differentiated in the present series.

Fig. 4. Embryo Ser. 24, 9 mms. Early splenic primordia in dorsal mesogastrium. Note small areas of early angiogenesis. x136.

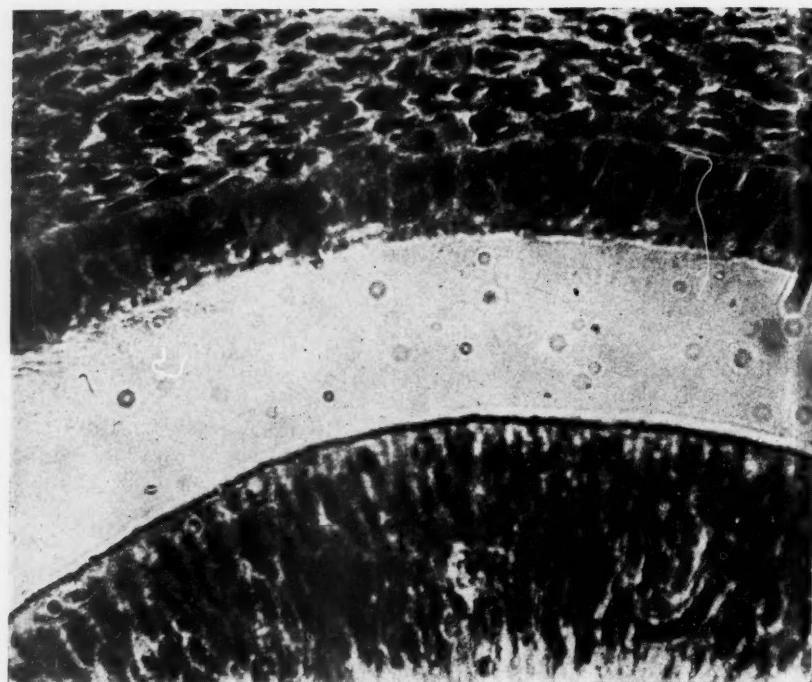


Fig. 6. Embryo Ser. 24, 9 mms. The outer layer of the retina shows no pigment granules. x460.

The following criteria showed this embryo to be a member of Horizon XV of Streeter. The lens vesicle was definitely closed (Fig. 3). There was no pigment in the outer layer of the retina. There was no migration of the inner retinal cell nuclei.

Embryo A (9 mms.) belonged to Horizon XV and showed an area of undifferentiated thickened mesenchyme in the left aspect of the dorsal mesogastrium, interpreted as early splenic primordia.

Embryo Ser. 24, 9 mms. (Collection of the Department of Histology, Karolinska Institutet), was likewise sectioned serially and transversely. It had been fixed in formalin. The sections are 10 microns thick and hematoxylin-eosin stained. The embryo is in excellent preservation.

In the thickened dorsal mesogastrium there was a bulge to the left. This thickened dorsal mesogastrium was well separated from the stomach wall by

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Fig. 7. Embryo Ser. 31, 9 mms. Early splenic primordia are seen in the thickened dorsal mesogastrium. x55.

a recess, similar to that described previously in Embryo A. In the thickened part there were small areas of angiogenesis (Fig. 4). No clear-cut sinusoids were present. The part of the dorsal mesogastrium described was considered to be early splenic primordia.

This embryo was also shown to be a member of Horizon XV. The lens vesicle was closed (Fig. 5). There was no pigment in the outer layer of the retina (Fig. 6). No evidence of migration of the inner retinal cell nuclei was present.

Embryo Ser. 24 (9 mms.) belonged to Horizon XV. It showed evidence of early splenic primordia in the left aspect of the dorsal mesogastrium with small areas of angiogenesis but without sinusoids.

Embryo Ser. 31, 9 mms. (Collection of the Department of Histology, Karolinska Institutet), was serially sectioned transversely after formalin fixation. The sections are 10 microns thick and hematoxylin-eosin stained. The embryo is in excellent preservation.

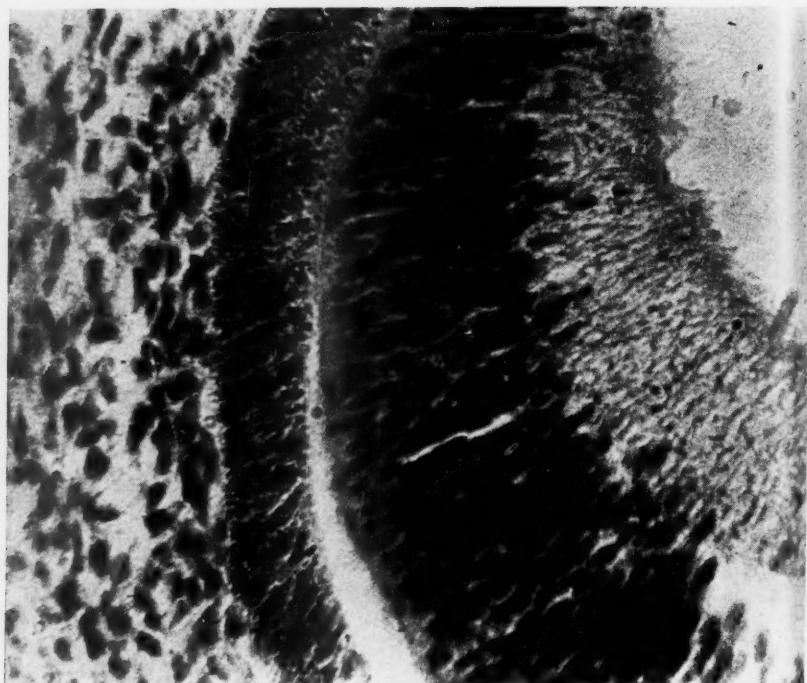


Fig. 8. Embryo Ser. 31, 9 mms. In the outer layer of the retina pigment granules without clustering or peripheral migration are seen. In the inner retinal layer there is no migration of nuclei. x675.

The dorsal mesogastrium was greatly thickened (Fig. 7). There was a bulge to the left. This area of bulging was considered to be early splenic primordia. Angiogenesis was clearly seen and was more prominent in this embryo than in the previously described Embryo Ser. 24. In addition, occasional small sinusoids lined with thin endothelium were encountered.

This embryo belonged to Horizon XVI. The lens vesicle was closed. There were pigment granules in the outer layer of the retina, without clustering or peripheral migration (Fig. 8). There was no migration of the inner retinal cell nuclei. The A—V canal cushions were fused. There was a primitive gut mesentery.

Embryo Ser. 31 (9 mms.) belonged to Horizon XVI. It contained splenic primordia in the left aspect of the dorsal mesogastrium. There were angiogenesis and small endothelium-lined sinusoids.

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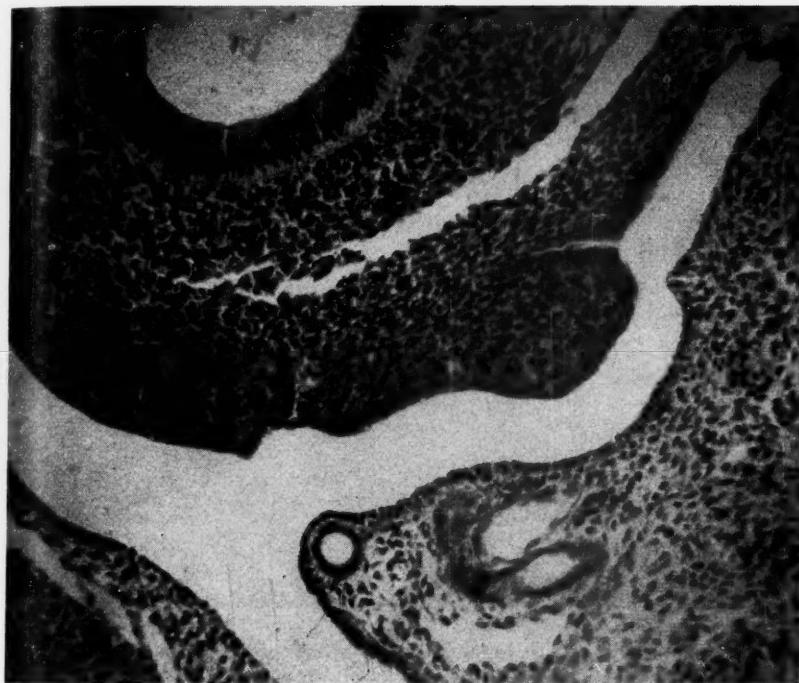


Fig. 9. Embryo No. 20, 9 mms. Splenic primordia in left aspect of dorsal mesogastrium. To the right there is a small incisure on the surface. x136.

Embryo No. 20, 9 mms. (Collection of the Department of Histology, Karolinska Institutet), was serially sectioned transversely after formalin fixation. The sections are 10 microns thick and hematoxylin-eosin stained. The embryo is in excellent preservation.

The left aspect of the dorsal mesogastrium was thickened. The early splenic primordia showed angiogenesis and there were occasional sinusoids present. On the surface there was evidence of early notching. In Fig. 9 an incisure is seen to the right. These splenic primordia appeared more mature than those described previously in this series.

The following characteristics showed the embryo to be a member of Horizon XVI. There were definite pigment granules in the outer layer of the retina (Fig. 10), without clustering or migration peripherally. In the inner retinal layer very occasional nuclei showed migration. The posterior lobe of

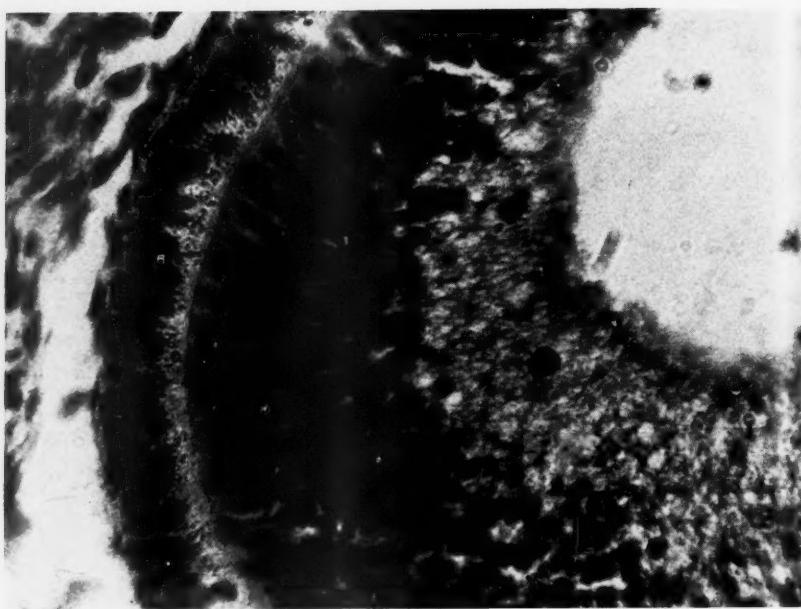


Fig. 10. Embryo No. 20, 9 mms. In the outer layer of the retina pigment granules without clustering or peripheral migration are seen. In the inner layer very occasional nuclei show migration toward the center of the eye. x675.

the pituitary was beginning to evaginate. The A—V canal cushions were fused. There was an epithelial bronchial tree and a primitive gut mesentery.

Embryo No. 20 (9 mms.) belonged to Horizon XVI. Splenic primordia were present in the left aspect of the dorsal mesogastrium, with evidence of notching. There were angiogenesis and small sinusoids.

Embryo Ser. 10, 11 mms. (Collection of the Department of Histology, Karolinska Institutet), was serially sectioned sagittally at 5 microns after fixation in formalin. It is hematoxylin-eosin stained. It shows excellent preservation.

The dorsal mesogastrium contained a bulge to the left (Fig. 11). In this area, considered to be the splenic primordia, there was prominent angiogenesis. Several sinusoids lined with endothelium were present. This early spleen was the most differentiated of the splenic primordia described in this series.

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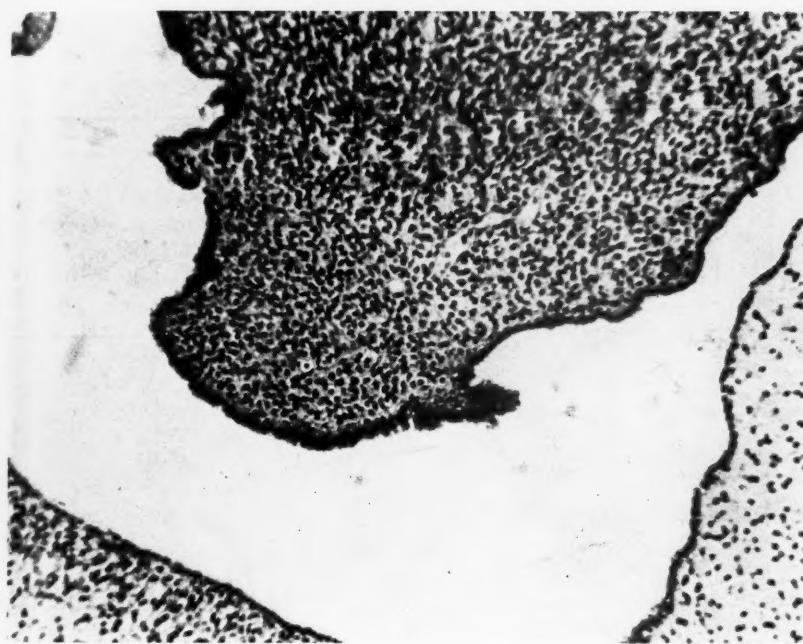


Fig. 11. Embryo Ser. 10, 11 mms. Splenic primordia with prominent angiogenesis and early sinusoids. $\times 136$.

The following criteria showed this embryo to be a member of Horizon XVII. There were pigment granules in the outer layer of the retina with clustering and migration peripherally (Figs. 12-13). Migration of some of the inner cell nuclei had occurred in the retina (Fig. 12). The A-V canal cushions were fused. In the bronchial tree there was evidence of branches of secondary order, the initiation of pulmonary lobation. There were well marked calyces in the kidneys.

Embryo Ser. 10 (11 mms.) belonged to Horizon XVII. Splenic primordia, with prominent angiogenesis and several sinusoids, were present. These primordia appeared to be the most mature in the series described.

Embryo Ser. 32, 12 mms. (Collection of the Department of Histology, Karolinska Institutet), was serially sectioned transversely after formalin fixation. The sections are 10 microns thick and hematoxylin-eosin stained. The embryo is in excellent preservation.



Fig. 12. Embryo Ser. 10, 11 mms. In the outer layer of the retina there are pigment granules with clustering and peripheral migration. The inner retinal cell nuclei show migration toward the center of the eye. x675.

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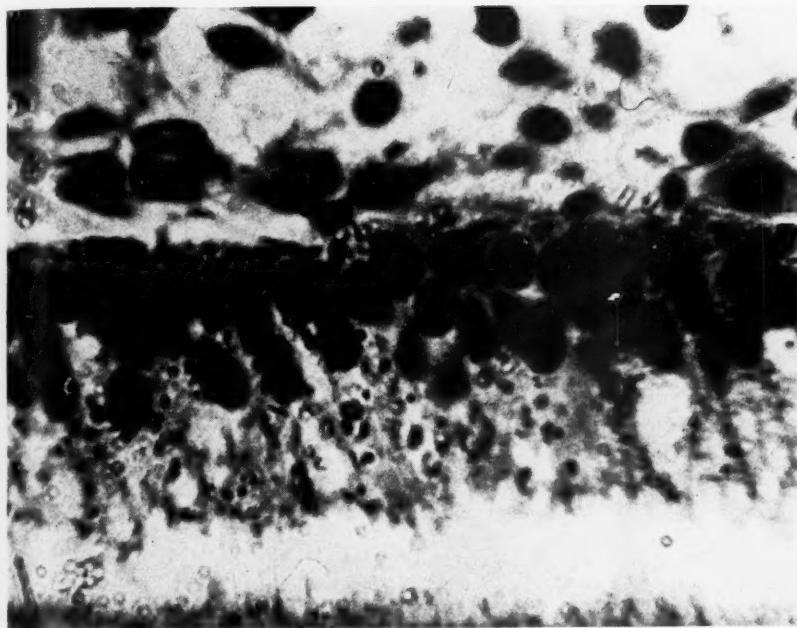


Fig. 13. Embryo Ser. 10, 11 mms. The pigment granules in the outer layer of the retina show clustering and peripheral migration. $\times 1020$.

The left aspect of the dorsal mesogastrium was greatly thickened (Fig. 14). The early splenic primordia were the site of angiogenesis (Fig. 15), and there was cellular condensation in this area as compared with the stomach wall. A few sinusoids were encountered

This embryo belonged to Horizon XVI. There were pigment granules in the outer retinal layer, without clustering or migration toward the periphery (Fig. 16). There was no migration of the inner cell nuclei of the retina. The posterior lobe of the pituitary was beginning to evaginate. The A-V canal cushions were fused. In the bronchial tree no clear-cut branches of secondary order were found. There was a primitive gut mesentery.

Embryo Ser. 32 (12 mms.) belonged to Horizon XVI. There were splenic primordia with angiogenesis and a few sinusoids. This embryo was less mature, morphologically, than Embryo Ser. 10, previously described.

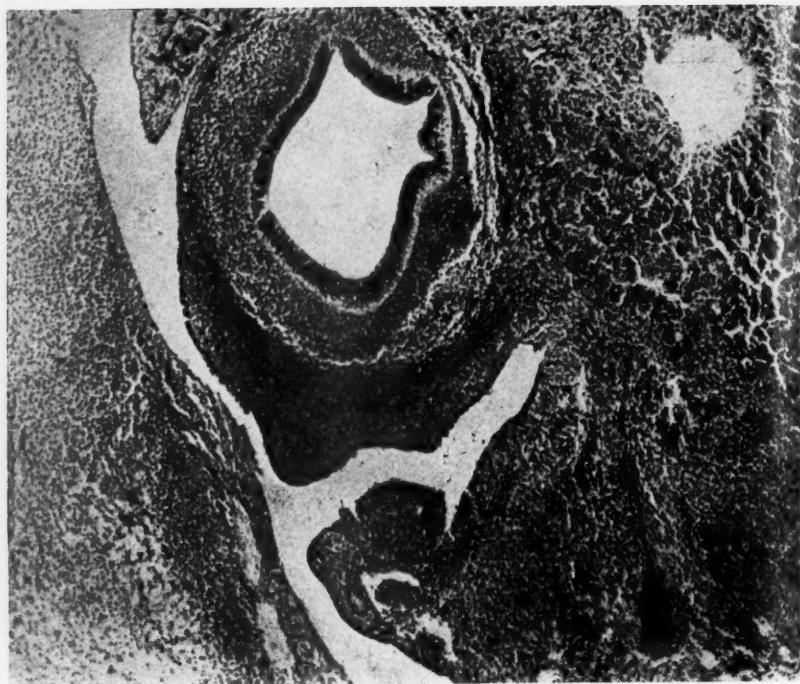


Fig. 14. Embryo Ser. 32, 12 mms. The splenic primordia are seen in the left aspect of the dorsal mesogastrium in lower center of picture. x38.

In summary, splenic primordia have been shown to be present in six human embryos belonging to Horizons XV—XVII. The first morphologic evidence of such primordia consists of an area of mesenchymal thickening in the dorsal mesogastrium. This occurs in Horizon XV. Small areas of angiogenesis but no sinusoids may be found in this horizon. In Horizon XVI there is evidence of increasing angiogenesis, and the first sinusoids appear. In Horizon XVI, as seen in one embryo (No. 20), there may be incisures of the surface of the splenic primordia. In Horizon XVII sinusoids are more prominent.

These findings are in accordance with statements in the literature. *Arey* (1954) describes the swelling of the dorsal mesogastrium as occurring in embryos of 8 mms. greatest length. *Broman* (1927) gives the greatest length as 10 mms. *Kollmann* (1907) states that the length is 10.5 mms.; *Hamilton, Boyd & Mossman* (1952), 10 mms.; and *Starck* (1955), 10 mms.

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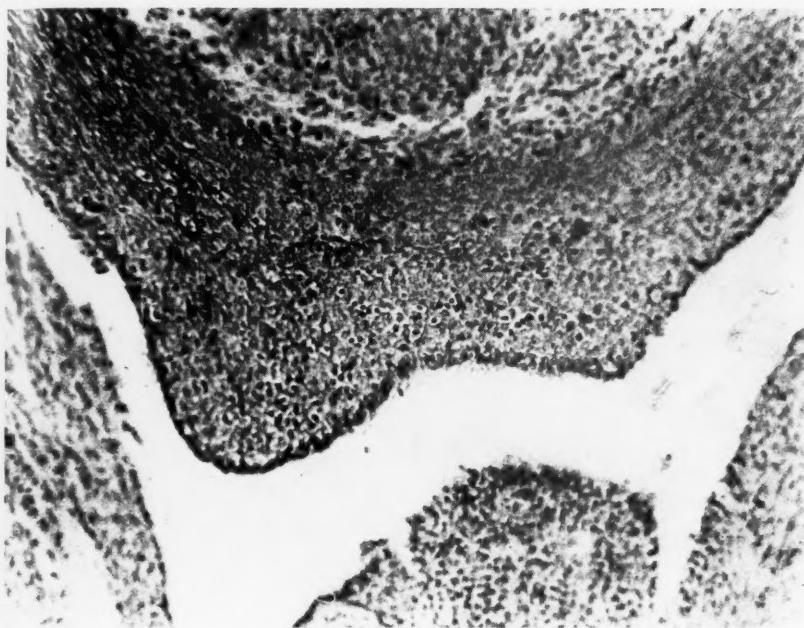


Fig. 15. Embryo Ser. 32, 12 mms. Higher magnification of splenic primordia. Angiogenesis is evident. x136.

The notching of the surface is said by *Broman* (1921) to occur in the latter part of the third embryonal month. However, in one of the human embryos described by the writer, incisures appeared in Horizon XVI. This would correspond to an ovulation age of 32—34 days. *Clatworthy & Anderson* (1944) state that the mesenchyme in the dorsal mesogastrium starts to proliferate and becomes vascularized in the sixth embryonal week, and that blood spaces and notching form in the third embryonal month. The varying figures for the greatest length of the embryo at the time of the appearance of the splenic primordia are evidence for the usefulness of the horizontal concept of *Streeter* as far as the estimation of the developmental level is concerned.

As the earliest discernible stage of spleen formation appears to be a swelling of the dorsal mesogastrium and a condensation of its cells, the morphologic evidence of the presence of the "first" splenic *anlage* by definition is subjective and unreliable. It seems very likely that histochemical

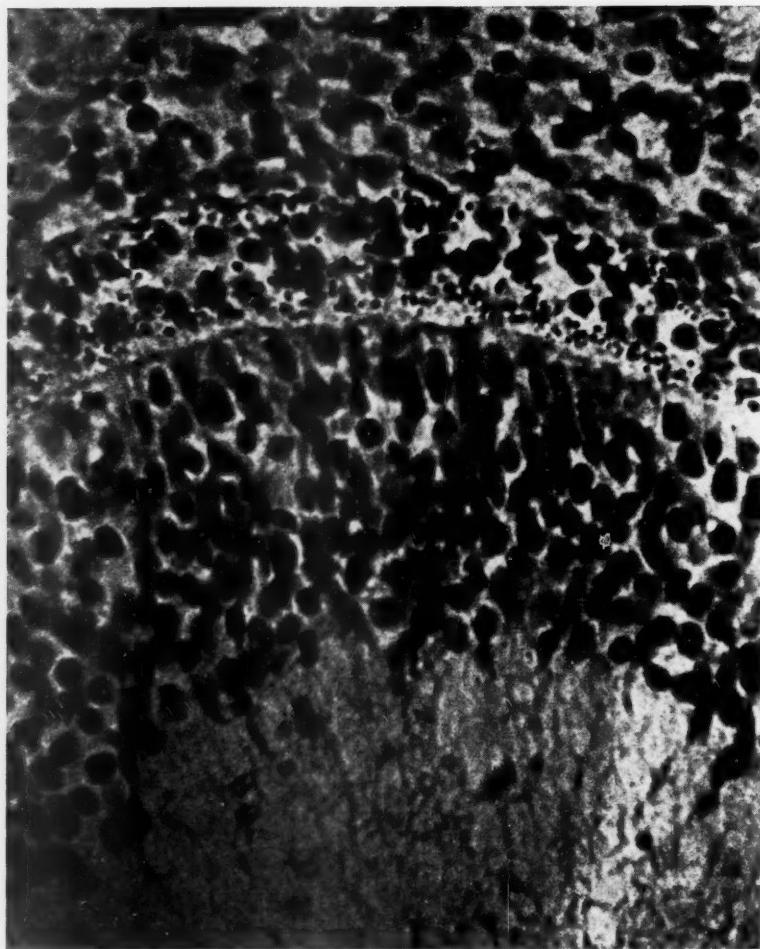


Fig. 16. Embryo Ser. 32, 12 mms. In the outer layer of the retina pigment granules without clustering or migration are seen. In the inner layer there is no evidence of nuclear migration. x675.

methods would enable us to locate the splenic primordia even earlier, if there were a known specific stainable substance in them. Besides, in formalin fixed, paraffin embedded and hematoxylin-eosin stained preparations no histochemical studies are possible. However, as the spleen is known to grow

very rapidly (*Patten*, 1953 a), it seems probable that it is in its early formative stage in Horizons XV—XVI. The exact dating of the earliest appearance of the splenic primordia would need a large material and would call for various techniques for exact localization, for example, analogous with the histochemical studies on germ cells by *McKay et al.* (1953).

As the early formative stage of splenic organogenesis can be assumed to occur around Horizon XVI, this part of embryogenesis will be reviewed briefly. Particular attention will be paid to the cono-truncus and the atrio-ventricular canal, as the interrelation of these structures forms the body of this paper.

B. On the Morphogenesis of the Cono-Truncus and the A-V Region at the Time of Early Splenic Organogenesis

In the following sections *Streeter's* timing of embryos will be adopted. Other systems of dating early embryos have been published by, for example, *Patten* (1953 a). *Streeter's* (1948) criteria for *Horizon XV* were deduced from data on 25 embryos, 18 of which had a greatest length varying from 6.5—8.5 mms. The estimated ovulation age was between 31 and 32 days as calculated from comparisons with macaque embryos of known ovulation age. This method of estimation of age was the same in all horizons to be described.

The criteria for *Horizon XVI* were obtained on 36 embryos, 24 of which had a greatest length of between 8 and 11 mms. The calculated ovulation age was 33 ± 1 days for the group.

Horizon XVII was composed of 25 embryos, 17 of which had a greatest length of 11.0 to 13.6 mms. The calculated ovulation age was 35 ± 1 days.

Horizons XV, XVI, and XVII are thus separated by approximately two days each. During the six days covered by Horizons XV—XVII, the early splenic primordia have been shown to exist. As will be pointed out later, the critical modeling of the cono-truncus and the atrio-ventricular canal occurs at this time in embryogenesis.

On the division of the cono-truncus

According to *Streeter* (1948), the spiraling septum dividing the truncus arteriosus starts to grow from the distal end of the truncus during the XVth Horizon, is well under way but not completed in Horizon XVI, and separates the pulmonary trunk from the aorta in Horizon XVII. The septum is formed by ingrowth of the gelatinous reticulum of *Streeter* (*Kramer* 1942; *Streeter*, 1948; *Patten*, 1953 b), a descriptive term preferred by the writer to the

"embryonal connective tissue" or the "endocardial cushion tissue" used by other authors. The cardiac jelly (*Davis*, 1924 and 1927) is converted to gelatinous reticulum when it shows evidence of cells, *i.e.*, nuclei.

That the truncus septum is spiral in its growth is well established (*e.g.*, *Kramer*, 1942). Whether the spiraling course is genetically determined or whether hemodynamics plays a part in its modeling is, however, still controversial. Self-differentiation of explanted or heterotopically transplanted hearts deprived of their circulation has been demonstrated in numerous publications (for references, see *Copenhaver*, 1955). The explanted hearts have been reported as not being old enough, however, to display differentiation of the cono-truncus, and it is not yet known whether self-differentiation and septation of the cono-truncus can occur in hearts lacking blood circulation. *Stöhr* (1925) and *Bremer* (1928 and 1931) have shown in amphibians and birds that the blood stream has an effect on the differentiation of the cono-truncus in the later stages of development. *Streeter* (1948) stresses the possible influence of the two blood streams in the division of the cono-truncus. *Patten*, *Kramer & Barry* (1948) agree with *Bremer* that the spiraling blood streams may have a molding effect on the gelatinous reticulum, leading the course of its growth into septa. This slack-water theory of septation was mentioned by *Spitzer* (1919) and *Beneke* (1920), but extended and further elaborated by *Bremer* (1931) who observed spiraling blood streams in the heart of the living chick embryo, and who studied these currents in hollow glass models of chick embryo hearts.

The idea of using glass models of hearts for the study of blood circulation is not new. *Leonardo da Vinci* (quot. *Bremer*, 1931) was probably the first to suggest this mode of approach. Valuable information on the course of blood currents within the developing heart has been obtained since *Bremer* in 1931 introduced the method in actual practice (*Romhányi*, 1952; *Kl. Goerttler*, 1954 and 1955). In brief, there is evidence of spiraling currents of blood that do not mix and that exist before septation is accomplished, or even started. There are areas of lessened lateral pressure ("seitendruckfreie Zonen" of *Goerttler*) between these spirals along which the future septa will grow. This is indirect evidence that blood currents play some role as causative factors, at least for the septation of the cono-truncus, and possibly for the atrio-ventricular canal. The spirally twisted streams have been recorded in motion pictures, first by *Patten* (quot. *Bremer*, 1931) and later by others (*Bremer*, 1931; *Kl. Goerttler*, 1954 and 1955).

Genetic factors and the appearance of two blood streams spiraling around each other do not seem to be the sole factors in operation during the separation of the cono-truncus. *Bremer* (1931) encountered one chick embryo

heart that showed spiral ridges in the conus despite the fact that blood entered the heart only from the right vitelline veins. Thus, there was only one blood stream traversing the heart. The explanation of this observation seems to lie in the shape of the entire cono-truncus.

Since 1938, *Doerr* has emphasized the importance of the form of the cono-truncus for the understanding of its septation, normal or abnormal. In 1955, *Doerr* (1955 a) summarized his concept of various anomalies of this region, and stressed the normal migration of the cono-truncus, the "vectorial conus torsion" ("vektorielle Bulbusdrehung") as having three components: a) migration of the conus from right to ventral, b) torsion of the truncus along its longitudinal axis, and c) angular bending ("Abknickung") of the conus from right and ventral to left and dorsal. Because of this bent form of the cono-truncus the spiralization of the blood streams is maintained in this region of the heart (*Kl. Goettler*, 1954).

The vectorial torsion of the cono-truncus is, in other words, a prerequisite for the spiraling of its blood currents. This appears to be of fundamental importance for the understanding of the growth of the truncus septum, and would serve as a tenable explanation of *Bremer's* finding of spiral ridges in the conus in the presence of only one blood stream, as noted above.

The aortic and pulmonary valves

These are initiated in the XVIIth Horizon in the form of condensations of the gelatinous reticulum (*Streeter*, 1948). These structures are not valves in the morphologic sense but apparently function with a valve-like action (*Patten, Kramer & Barry*, 1948). In the XVIIIth Horizon, when the separation of the truncus is complete, the club-shaped semilunar valves are distinguishable (*Streeter*, 1948). In the older members of this age group, the crest of the interventricular septum fuses with the truncus septum to make up the membranous part of the interventricular septum, closing it in the latter part of Horizon XVIII, when the embryo is about 37 days old (*Streeter*, 1948).

On the division of the atrio-ventricular canal

It is generally agreed that the partitioning of the atrio-ventricular canal is accomplished by fusion of three structures, the two endocardial cushions and the septum primum (e.g., *Patten*, 1953 a and b). The closure of the membranous interventricular septum is accomplished later, and does not *per se* participate in the division of the canal proper.

The early contact between the dorsal and ventral endocardial cushions of the atrio-ventricular canal is established in Horizon XVI (*Streeter, 1948*). Thus, two morphologically distinct channels are produced in this region before this occurs in the conus. The differentiation of the atrio-ventricular canal cushions into valves is, however, conspicuously later than the differentiation of the aortic and pulmonary valves. The mitral and tricuspid channels show only condensed gelatinous reticulum in Horizon XVIII when the aortic and pulmonary valves are morphologically distinct (*Streeter, 1948*), and the atrio-ventricular valves are not differentiated until later (Horizon XIX, *Streeter, 1951*).

Although differentiation of the heart generally proceeds in a cephalo-caudad direction, from the conus to the sino-atrial region, it is interesting to note that the division of the atrio-ventricular canal is accomplished before completion of the morphologic division of the cono-truncus into separate aortic and pulmonary channels. Possibly the fusion of the dorsal and ventral atrio-ventricular canal cushions facilitates the normal migration of the conus.

Doerr (1952, a and b) has pointed out the close interrelation between the cono-truncus and the atrio-ventricular canal, inasmuch as the aortic part of the cono-truncus migrates in close proximity to the right atrio-ventricular ostium. *Doerr* further maintains that the migration of the cono-truncus is responsible for the asymmetric shaping of the atrio-ventricular ostia into tricuspid right and bicuspid left. *Doerr* coins the term "conflict zone" ("Konfliktzone") for the area between the ventral aspect of the atrio-ventricular ostium and the dorsal aspect of the conus. The term conflict zone implies a region where there is normally an intimate relationship between organs or structures, and where in pathologic conditions essential developmental errors may develop. The understanding of the normal interrelations of structures in these conflict zones is essential for comprehensive grasping of malformations in these regions. The conflict zone between the conus and the atrio-ventricular region is considered by *Doerr (1952 a)* to be the Achilles heel of the normal migration of the conus.

Summary

- a) Early splenic primordia in six human embryos have been shown to be present in Horizons XV to XVII of *Streeter*, when the embryo has an estimated ovulation age of 31—36 days.
- b) The fusion of the atrio-ventricular canal cushions occurs in the XVIth

- Horizon, while the complete separation of the cono-truncus is accomplished about two days later, in the XVIIth Horizon (Streeter, 1948).
- e) The importance of spiraling blood currents in the septation of the cono-truncus has been brought out (Bremer; Patten, Kramer & Barry; Romhányi; Kl. Goertler).
 - d) The shape of the cono-truncus as determining the spiralization of the blood of this part of the heart has been stressed (Doerr).
 - e) The interrelationship between the cono-truncus and the atrio-ventricular canal in the form of a "conflict zone" is emphasized (Doerr).

PART II

Congenital Malformations of the Heart and Great Vessels Associated with Congenital Asplenia

A. Historical Review

Congenital malformations of the heart and great vessels coexistent with agenesis of the spleen have long been looked upon as a great rarity. In the past it was the pathologist who very occasionally encountered this combination of anomalies. The first two cases on record are those of *Martin* and *Breschet* who in 1826 described the autopsy findings of septal defects, transposition of the great arteries and agenesis of the spleen. In addition, the case of *Breschet* showed pulmonary atresia.

During the nineteenth century and the first three decades of the twentieth century, occasional reports dealt with cardiac anomalies associated with agenesis of the spleen. In 1934 *Putschar* summarized the findings in all cases, including adults, reported to that time. That author collected from the literature reports on autopsies of 22 infants and children affected with this anomaly, and added a stillborn case of his own. All these were associated with various anomalies and 20 displayed definite malformations of the heart and/or great vessels.

Putschar stresses the frequent occurrence of malformations of the heart and great vessels in cases of agenesis of the spleen. He points out the common finding of abnormal septation of the heart and the occurrence of transposition of the great arteries occasionally associated with atresia or stenosis of the pulmonary trunk. Further, *Putschar* stresses the fact that many cases show abnormal systemic and/or pulmonary venous connections. *Putschar's* main interest focuses on their association with situs inversus, and he groups the cases according to this manifestation of dysontogenesis.

On the cause of the absence of the spleen *Putschar* does not comment. He mentions the possibility that, either there was a complete agenesis, or there had been a disappearance of the splenic primordia after they had been formed. *Putschar* suggests that events leading to the malformation started in approximately the third to fourth week of embryonic life, and adds that even a later date might be considered, if one should count on a complete atrophy of the splenic primordia after they had been formed.

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Among cases not mentioned by *Putschar*, reference might be made to a few. In 1927, *Garvin* gave a short description of a child with *cor biloculare*, *truncus communis*, and drainage of the pulmonary veins into the superior vena cava associated with agenesis of the spleen. In 1932, *Behr* described the findings in a 2½-year-old girl. There were dextrocardia, *cor biloculare*, transposition of the great arteries, pulmonary atresia, persistent ductus arteriosus, and agenesis of the spleen. In the same year, *Kugel* reported the autopsy findings in a 4-month-old male with dextrocardia, *cor biloculare*, pulmonary atresia, partially anomalous venous connections, symmetric liver, transposed stomach, and absence of the spleen.

Since *Putschar's* paper appeared, scattered reports have been encountered in the literature. Concerning these the reader is referred to the tables at the end of this paper where the anatomic features are summarized.

The first to review the literature after *Putschar* were *Polhemus & Schafer* (1952). These authors reported four of their own cases, and stressed, for the first time, the syndromic character of cases of cardiac malformation associated with absence of the spleen. *Polhemus & Schafer* considered an *ostium atrio-ventriculare commune* to be the common denominator of the syndrome. The four cases reported by *Polhemus & Schafer* are all very similar to those mentioned above. Thus, three showed *cor biloculare*, one of which had pulmonary atresia, and another two, pulmonary stenosis. The fourth case had an *ostium primum* with persistent atrio-ventricular canal. One of the cases showed dextrocardia, and all displayed three-lobed lungs, bilaterally.

The first two cases of agenesis of the spleen associated with congenital heart disease to be diagnosed clinically, were reported by *Gasser & Willi* (1952). The authors gave an account of the clinical, including hematologic, findings in two cyanosed infants. There was a persistently increased number of Heinz bodies in the erythrocytes of the peripheral blood. The authors made the clinical diagnosis of congenital heart disease associated with agenesis of the spleen. Their diagnoses were confirmed at autopsy. Bilocular hearts with *truncus communis* and pulmonary atresia, respectively, were found. They referred to the case reported by *Fueter* (1938) and *Töndury* (1936, same case as *Fueter's*, abdominal organs reported) and stressed the similarities between the three cases. *Gasser & Willi* suggested that an endogenous lethal factor with pleiotropic effects had been at work to cause the association of anomalies.

Subsequently, a few cases have been reported (*Adler & van Slyke*, 1953; *Boggs & Reed*, 2 cases, 1953; *Campbell & Forgaes*, 1953; *Campbell et al.*, 2 cases, 1953; *Baumann*, 2 cases, 1954; *Bush & Ainger*, 1955; *Willi & Gasser*,

Case 4, 1955). The two cases reported by *Campbell et al.* (1953) and Case 9 of *Campbell & Forgaes* (1953) are remarkable as they are the oldest ever found, being 4, 8, and 5 years of age at the time of death, respectively.

For further details concerning the above-mentioned cases the reader is referred to the tables at the end of the paper.

B. Material

The material consists of 69 cases. Fifty-five have been collected from the literature, and 14 new cases have been added. Only reports with autopsy findings have been included.

Sixty-five cases show recorded anomalies in the cono-truncus region. As the purpose of this paper is to analyze the pathogenesis of malformations of the cono-truncus area of the heart, for practical purposes all cases have been grouped according to the various malformations of that region. Thus,

Type A represents cases of agenesis of the spleen with persistent truncus arteriosus;

Type B, cases of agenesis of the spleen with pulmonary stenosis or atresia, with or without transposition of the great arteries;

Type C, cases of agenesis of the spleen with transposition of the great arteries without pulmonary stenosis or atresia, and

Type D, cases of agenesis of the spleen without reported anomalies in the cono-truncus region.

The types have been chosen in this order in an attempt to cover the cases in an ontogenetic order of development. Hence, cases belonging to Type A represent more primitive forms than those of type B; i.e., embryologically, the development of the cono-truncus is assumed to have been disturbed earlier in Type A.

Type A. Cases of agenesis of the spleen with persistent truncus arteriosus

Definition. In this paper, a persistent truncus arteriosus is defined as the only artery leaving the ventricular portion of the heart without remnants, factual or implied, of any other arterial vessel. From this common artery emerge the coronary arteries, the branches of the arch and the pulmonary arterial supply (pulmonary or bronchial arteries, but not a ductus arteriosus). Thus, the definition of *Edwards* (1953 a) is followed. The material does not permit an ontogenetically adequate classification into "ideal truncus" of *Humphreys* (1932), or into aortic or pulmonic "pseudo-truncus" of *Doerr* (1955 b).

Material. Ten cases show this anomaly. Six cases have been collected from the literature (*Krausse*, case 2, 1905; *Garvin*, 1927; *Kimura*, 1930; *Shapiro*,

1930; *Gasser & Willi*, case 1, 1952; and *Baumann*, case 1, 1954). For details concerning these cases, see Table A at the end of the paper.

The author adds four cases: Nos. 1, 2, 3, and 10. The case reports are found at the end of this section.

Type B. Cases of agenesis of the spleen with pulmonary stenosis or atresia, with or without transposition of the great arteries

Definition. The pulmonary stenosis may be valvular or infundibular. Atresia denotes that the pulmonary trunk ends blindly in the myocardium from above, or that it is converted into a fibrotic strand of tissue without a lumen.

Transposition of the great arteries denotes an abnormal relationship to each other of the arterial trunks at their respective points of origin in the heart.

Material. Thirty-four cases from the literature and seven new cases belong to this type. Six cases show stenosis without transposition (*Krausse*, case 1, 1905; *Feldmann*, 1930; *Polhemus & Schafer*, cases 1 and 2, 1952; *Boggs & Reed*, case 2, 1953; *Author*, case 7).

Thirteen cases show transposition in addition to stenosis (*Kundrat*, 1887; *Gardère*, 1908; *Hu*, 1929; *Behr*, 1932; *Conn, Clark & Kissane*, case 4, 1950; *Lüdin*, 1952; *Polhemus & Schafer*, case 3, 1952; *Campbell, Reynolds & Trounce*, 2 cases, 1953; *Campbell & Forgacs*, case 9, 1953; *Author*, cases 4, 13, and 14).

Twenty-two cases display atresia of the pulmonary trunk (*Breschet*, 1826; *Arnold*, 1868; *Rokitansky*, case 1, 1875; *Geipel*, 1899; *Kugel*, 1932; *Gerstenberger*, 1938; *Lightner*, 1939; *Durie & Wyndham*, case 1, 1942; *Roszman*, 1942; *Young*, 1947; *Weinberg & Kolson*, 1949; *Leikin*, 1951; *Polhemus & Schafer*, case 4, 1952; *Gasser & Willi*, case 2, 1952; *Adler & van Slyke*, 1953; *Boggs & Reed*, case 1, 1953; *Baumann*, case 2, 1954; *Bush & Ainger*, 1955; *Willi & Gasser*, case 4, 1955; *Author*, cases 6, 9, and 12).

Thus the author contributes seven cases of this type: Nos. 4, 6, 7, 9, 12, 13, and 14. The case reports are found at the end of this section.

Type C. Cases of agenesis of the spleen with transposition of the great arteries without pulmonary stenosis or atresia

Definition. Transposition is taken in its widest sense, denoting any abnormality in the relationship in position between the arterial trunks at their points of origin in the heart. Subdivision into groups of more or less complete transposition, or corrected transposition, has not been made.

Material. Fourteen cases show this pattern. Eleven cases have been found in the literature (*Martin*, 1826; *Epstein*, 1886; *Kundrat*, 1888; *Lawrence & Nabarro*, 1901; *Mönckeberg*, 1915; *Pernkopf*, cases 4 and 5, 1926; *Fuetter*, 1938—the same case also reported by *Töndury*, 1936; *Taussig*, 1939; *Duvie & Wyndham*, case 2, 1942; *Jaccard*, case 1, 1951).

The writer adds three cases: Nos. 5, 8, and 11. The case reports are found at the end of this section.

Type D. Cases of agenesis of the spleen without reported anomalies in the cono-truncus region

Definition. In the case reports the truncus region has either been reported to be normal, or no description of this area is included in the reports accessible to the author.

Material. Four cases have been classified in this group. The author does not add any case.

Valleix's (1834) original case report has not been accessible to the writer. According to *Putschar* (1934) there was situs inversus of the heart, but no further description is given of the large arteries. This could mean that there was transposition of the great arteries; but, as not detailed description is available, by definition the case has to be grouped into this category.

Another case was reported by *Birch-Hirschfeld* (1871). This author specifically states that the great arteries are normal.

In *Bossert & Leichtentritt's* (1920) survey of bacteriologic findings in infants with various infections, one case of meningitis in a 9-month-old child (sex not given) is mentioned briefly (p. 182). At autopsy, absence of the cardiac septa with a suggestion of a four-chambered heart was found. The great arteries are not mentioned in this short report.

McLean & Craig (1922) state that the great arteries are normal in their case, a 3-month-old male with septal defects and inversion of the sino-atrial region.

Thus, in the literature there are at least two cases without anomalies of the cono-truncus region (*Birch-Hirschfeld*, 1871; *McLean & Craig*, 1922). Two other cases (*Valleix*, 1834; *Bossert & Leichtentritt*, 1920) are uncertain.

Case reports

In the following case reports the emphasis is laid on the gross pathology of the heart and great vessels. Only exceptional histologic data will be presented, and the cause of death in each instance will not be discussed. As the hearts were largely preserved for future study, routine sections were

not taken, for example, from atretic pulmonary valves. Only a minimum of clinical data will be included. The cases have been numbered according to age, and the Boston Children's Hospital cases (C.H.) are intermingled with other cases from various sources.

1. Type A

Four new cases belong to this category: Nos. 1, 2, 3, and 10.

Case 1

(Sabbatsbergs Sjukhus, O. 100/54). Stillborn. Uneventful pregnancy. The fetus was known to have been dead two weeks prior to delivery. Birth weight, 1,520 grams; body length, 43 cms.

Autopsy. *Peritoneal cavity.* The liver was symmetric, the left lobe equaling the right in size and occupying the left upper quadrant. The gall bladder was in the midline. The stomach was to the left of the midline. The spleen was absent. *Heart, lungs and great vessels.* The heart was of normal size, and the apex was pointing to the left. The heart was globular in shape. The lungs were composed of three lobes each. The inferior vena cava entered the right atrium, as did the superior vena cava. There were two right pulmonary veins entering the right atrium, and two left pulmonary veins that entered the left atrium. The coronary sinus opened into the right atrium. For practical purposes there was a single atrium with a rudimentary posterior septum. There was a common atrio-ventricular ostium with four cusps. The ventricular septum was absent. The only arterial vessel leaving the common ventricle was the aorta, which had three well formed leaflets. It arched over the left bronchus and gave off normal branches to the arms and the head. The last two branches of the arch consisted of two enlarged bronchial arteries, one to each lung, and leaving the aorta in its descending portion. There was no remnant of a pulmonary trunk, nor was there any evidence of a ductus arteriosus. Thus, there was a persistent truncus arteriosus (Type 4, Edwards, 1953 a). The coronary arteries were normal.

Anatomic diagnoses: Cor biloculare; levocardia; 4-cuspid A—V valve; persistent truncus arteriosus, with bronchial artery supply to lungs; anomalous pulmonary venous connection, partial, the right pulmonary veins connected to the right atrium; trilobed lungs; symmetric liver; agenesis of spleen.

An embryologic interpretation (Doerr, 1955 b) of the truncus in this case would be: Agenesis of the pulmonary trunk with bronchial artery supply to the lungs.

Case 2

L.C. (C.H. A-50-87). 3-day-old white male infant, the product of an uneventful pregnancy, labor and delivery. Cyanosis and respiratory distress developed on the second day of life, following attempts at feeding with water. The infant was admitted with a diagnosis of tracheo-esophageal fistula. The patient died 30 hours after admission at the age of 3 days.

Clinical impression: Question of intracranial hemorrhage; question of congenital heart disease.

Autopsy. Peritoneal cavity. There was partial situs inversus of the abdominal organs. The stomach was found in the right upper quadrant with the great curvature to the right and the pyloro-duodenal junction to the left. The duodenum, the head of the pancreas and the foramen of Winslow were in the left upper quadrant. The liver was symmetric, the left lobe equaling the right in size. The gall bladder was found in the left lobe. The spleen was absent. The cecum and the appendix were in the right upper quadrant and the segment of the colon between the right and left flexures was redundant. The inferior vena cava was located to the left of the aorta.

Heart, lungs, and great vessels. There was levocardia and the lungs had three lobes each. The inferior vena cava entered the left atrium. There were two superior venae cavae and no innominate veins. The left superior vena cava entered the left atrium; the right superior vena cava, the right. The coronary sinus emptied into the right atrium. There were four pulmonary veins, all entering the left atrium. There was no evidence of a pulmonary trunk or any remnants thereof. Emerging from the ventricular portion of the heart was only one arterial vessel, furnished with three leaflets and being a truncus arteriosus arching over the right bronchus. From the distal and proximal portions of the arch two short thick arterial trunks arose, and from these, three arteries branched on each side. The most inferior artery on each side entered the lungs and constituted the pulmonary arterial blood supply. The middle arteries were subclavian arteries and coursed to the arms while the most superior branches were common carotid arteries. Thus, the branches of the arch divided symmetrically. The interatrial septum showed an ovoid defect in its lower, anterior portion, measuring 2×1.5 cms., and constituting a persistent ostium primum. Above this there was a small interatrial septal defect in the area of the foramen ovale, but without any valve. There was no interventricular septum, nor any evidence of a rudimentary ventricle. The common ventricle communicated with the atria by way of a common 4-cuspid atrio-ventricular valve, measuring 5 cms. in circumference. The cusps were somewhat asymmetrically placed; one, posterior and in the midline;

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Fig. 17. Case 2. In situ picture showing a persistent truncus arteriosus with the dilated right bronchial artery branching from the descending portion of the truncus. The right superior vena cava is seen anterior to the right bronchial artery.

one, on the left; and two, on the right. They were all translucent, without cleavage, and with sharply defined margins. The circumference of the valve of the truncus measured 2.5 cms. There were two coronary arteries, one taking its origin from behind the posterior and another from behind the right anterior leaflet. Their pattern was normal.

Anatomic diagnoses: Cor triloculare biventriculare with persistent ostium primum; interatrial septal defect, small; levocardia; 4-cuspid A-V valve; persistent truncus arteriosus, 3-cuspid, with bronchial artery blood supply to the lungs; symmetric branching of the right aortic arch; anomalous systemic venous connection, partial, inferior and left superior vena cavae entering left atrium; partial abdominal situs inversus with incompletely rotated bowel, dextroposition of stomach; symmetric liver; agenesis of spleen; trilobed lungs.

An embryologic interpretation of the truncus arteriosus of this case according to Doerr (1955 b) would be: Agenesis of the pulmonary trunk with double ductus arteriosus.

Case 3

S.F. (C.H. A-48—270). 4-week-old white female infant with intermittent cyanosis and dyspnea that appeared 6—8 hours after birth. On admission at the age of 4 weeks there was edema of the legs and hepatomegaly, together with episodes of cyanosis. During one of these attacks the patient expired a few days after admission, at the age of 4 weeks.

Clinical impression: Tetralogy of Fallot with right aortic arch.

Autopsy. Peritoneal cavity. The liver was symmetric, the left equaling the right lobe; the gall bladder was in the left lobe. The stomach was on the left. There was a common mesentery. The cecum and appendix were in the right lower quadrant. The spleen was absent. The pancreas was annular.

Heart, lungs and great vessels. The heart was shifted to the right although the apex pointed to the left. The lobation of the lungs was normal. The heart-lung preparation was used for an injection study and then digested. The following data are evident from the protocol. The inferior and superior vanae cavae entered the right atrium. There was no left superior vena cava. The veins draining the left lung were connected to the left atrium and those draining the right lung, connected to the right atrium. The pulmonary trunk was absent and only one arterial vessel emerged from the heart. There was a left aortic arch with normal branching. From the descending aorta two large bronchial arteries coursed, one to each lung. There was no ductus arteriosus. The right atrium was larger than the left. There were two bicuspid atrio-ventricular valves, the right measuring 4.5 and the left, 5.0 cms. in circumference. There was no interventricular septum. The truncus arteriosus was guarded by three leaflets, two of which were posterior. Two coronary arteries emerged from behind the anterior and left posterior leaflets, respectively. They branched normally.

Anatomic diagnoses: Cor triloculare biventriculatum; levocardia with a shift to the right; two bicuspid A—V valves; persistent truncus arteriosus (Type 4, Edwards, 1953 a); anomalous pulmonary venous connection, partial, the right pulmonary veins entering the right atrium; symmetric liver; common mesentery; agenesis of the spleen; otitis media, purulent, left.

An attempted *embryologic interpretation* (Doerr, 1955 b) of the truncus arteriosus in this case would be: Agenesis of the pulmonary trunk with bronchial artery supply to the lungs.

Case 10

A.C. (C.H. A-27—72). This 5-month-old white male was born 1 month prematurely after an uneventful pregnancy. The infant was born cyanotic, and the cyanosis was intermittent and more prominent on crying and cough-

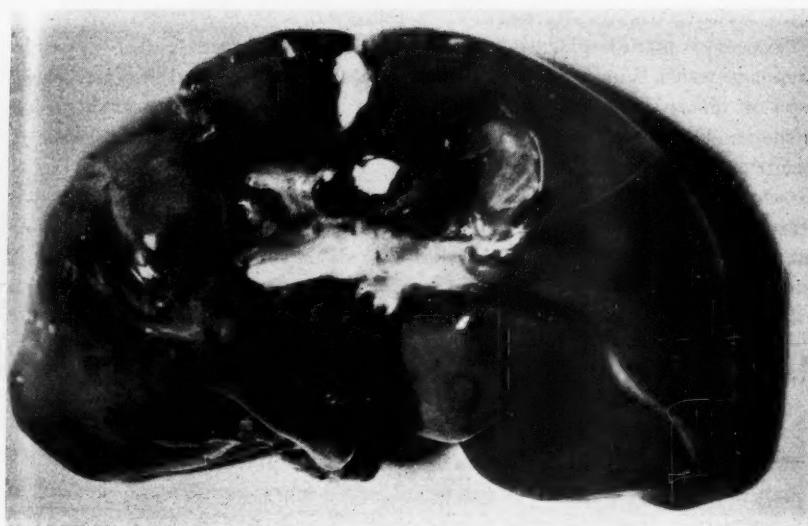


Fig. 18. Case 3. Symmetric liver, the left lobe equaling the right, with the former containing the gall bladder impression.

ing. At the age of 5 months he suddenly grew more cyanotic. On admission he was febrile and a roentgenologic examination revealed a malposition of the large bowel with signs of obstruction. The child expired shortly after an abdominal operation at the age of 5 months.

Clinical impression: Malrotation of large bowel; congenital heart disease.

Autopsy. Peritoneal cavity. The liver was transposed to the left; the stomach and the pancreas, to the right. There was a common mesentery running slightly obliquely from the upper right to the lower left quadrant. The spleen was absent. The left kidney was smaller than the right. There were post-operative adhesions surrounding an ileostomy. *Heart, lungs and great vessels.* There was dextrocardia, the apex pointing to the right. The lungs showed three lobes each with incomplete separation. The inferior and superior venae cavae and the coronary sinus entered the right side of the atrium. The right pulmonary veins were connected to the right, and the left pulmonary veins were connected to the left side of the atrium. There was only one artery leaving the ventricular portion, arching over the left bronchus and giving off the normal branches and furnishing the lungs with two large arteries from the descending portion. There was no remnant of a pulmonary trunk, nor

was there any ductus arteriosus. Thus, there was a Type 4 truncus arteriosus (*Edwards*, 1953 a). The interatrial septum was deficient, and the only remnant was a thin muscular band incompletely separating the atria. There was a bicuspid common atrio-ventricular valve and no interventricular septum. The truncus arteriosus emerged from the middle of this common ventricular cavity.

Anatomic diagnoses: Cor biloculare; dextrocardia; bicuspid common A—V valve; persistent truncus arteriosus (Type 4, *Edwards*, 1953 a); anomalous pulmonary venous connection, partial, the right pulmonary veins connected to the right atrium; abdominal situs inversus; common mesentery; agenesis of the spleen; hypoplasia of left kidney; trilobed lungs.

An embryologic interpretation of the truncus arteriosus in this case (*Doerr*, 1955 b) would be: Agenesis of the pulmonary trunk with bronchial artery supply of lungs.

2. Type B

Seven new cases belong to this category: Nos. 4, 6, 7, 9, 12, 13, and 14.

Case 4

P.A.B. (C.H. A-51-92). 1-month-old white female infant, the product of an uneventful pregnancy, labor and delivery. Shortly after birth cyanosis appeared. The cyanosis persisted in oxygen and progressed. At the age of one month she developed rapid respirations and more severe cyanosis and expired after a temporary improvement.

Autopsy. *Peritoneal cavity.* There was partial situs inversus of the abdominal organs with the stomach in the right upper quadrant with the great curvature lying laterally. The liver was symmetric, the left lobe equaling the right. The gall bladder was in the midline. The spleen was absent. There was a common mesentery running obliquely from the right upper to the left lower quadrant. The pancreas was freely mobile in the cavity with the tail along the lesser curvature of the stomach. *Heart, lungs and great vessels.* There was levocardia with a small, conically shaped heart. Each lung had three lobes. The inferior and superior venae cavae entered the right atrium. The pulmonary veins formed a common trunk that entered the superior vena cava. There was a valvular pulmonary stenosis, the valvular circumference measuring 1.3 cms. The pulmonary arteries were otherwise unremarkable and there was no ductus arteriosus. There was a right aortic arch with reversal of the great artery pattern. The right atrium was separated from the left only by a small crescentic band riding over a common atrio-

ventricular ostium measuring 4.5 cms. in circumference and furnished with four cusps. These were thin and translucent, but contained small firm nodules along the lines of closure. There was no interventricular septum, nor any rudimentary ventricle. The aorta arose from the common ventricle to the right of and somewhat anteriorly to the narrow pulmonary trunk. The aortic valve contained three leaflets and measured 3.2 cms. in circumference. The coronary distribution was normal.

Anatomic diagnoses: Cor biloculare; levocardia; right aortic arch; 4-cuspid common A-V valve; pulmonary stenosis, valvular; transposition of the great arteries; anomalous pulmonary venous connection, complete, to the superior vena cava; common mesentery; symmetric liver; dextroposition of stomach and pancreas; agenesis of the spleen; trilobed lungs.

Case 6

E.P. (C.H. A-46—58). 15-week-old female infant with cyanosis since birth. At 2 weeks of age dextrocardia with situs solitus of viscera was demonstrated. The cyanosis, which persisted, became more severe after a short period of improvement, and the patient died while en route to the hospital at the age of 15 weeks.

Clinical impression: Dextrocardia.

Autopsy. Peritoneal cavity. The liver was symmetric and the gall bladder was found to the left of the midline. There was a common mesentery furnishing the small bowel and the ascending and transverse portion of the large bowel. The great omentum was absent. The stomach was in the left upper quadrant. The spleen was absent. *Heart, lungs and great vessels.* There was dextrocardia, the apex of the heart pointing to the right. The lungs had three lobes each. The inferior vena cava entered the right atrium normally. Unfortunately, the superior vena cava was not dissected. The pulmonary veins all joined to form a common trunk that coursed parallel to the esophagus and pierced the diaphragm to join the portal vein. The pulmonary trunk was represented by a small thin thread of tissue lying to the left of and behind the aorta. It ended as a blind pouch in the myocardium; thus, there was pulmonary atresia. There was a right patent ductus arteriosus running in front of the trachea. There was a right aortic arch and right descending aorta. The branches of the arch were the mirror image of normal with a left innominate artery as its first branch. The right atrium was larger than the left; and in the lower, anterior portion of the interatrial septum there was a large crescentic defect constituting a persistent ostium primum.

There was a common atrio-ventricular ostium furnished with four cusps and measuring 3.3 cms. in circumference. The cusps did not show any cleavage. There was a common ventricle with a moderately prominent crista supraventricularis. The ventricular wall measured 0.8 cm. in thickness. The aorta arose from the center of this cavity and the valvular circumference was 2.7 cms. The coronary arteries were normal. The left atrium was small and received no pulmonary veins.

Anatomic diagnoses: Cor triloculare biastratum; dextrocardia; persistent ostium primum; 4-cuspid common A-V valve; pulmonary atresia with transposition of the great arteries; right aortic arch and right descending aorta; patent right ductus arteriosus; anomalous pulmonary venous connection, complete, to portal vein; common mesentery; symmetric liver; agenesis of the spleen; trilobed lungs; bronchopneumonia, acute, hemorrhagic.

Case 7

M.J.S. (Walter Reed Army Hospital, A-5779). This 4-month-old white male was the product of an uneventful pregnancy and delivery at full term. He was cyanotic at birth. Gradually, episodes of respiratory distress appeared following feeding. During one of these episodes the child expired at the age of 3 months and 25 days.

Clinical impression: Congenital heart disease, incompletely diagnosed.

Autopsy. Peritoneal cavity. The liver extended to the left flank and was enlarged, weighing 229 grams. The gall bladder was absent, but the bile ducts were normal. The stomach was in the right upper quadrant and the cardia was located to the right of the vertebral column. The pancreas was resting on the anterior aspect of the stomach wall, and attached to a rudimentary omentum. The bowel was normal in appearance. The spleen was absent. *Heart, lungs and great vessels.* The heart was globular and the apex pointed to the left. The lungs showed normal lobation. The inferior and superior venae cavae entered the right atrium and the pulmonary veins all entered the left atrium. There was a left aortic arch with normal branching. The ductus arteriosus was obliterated. The interatrial septum was deficient in its upper posterior portion, showing a widely dilated foramen ovale with a totally inadequate valve. The common atrio-ventricular valve had three atrophic cusps, and measured 5.0 cms. in circumference. There was a common ventricle without evidence of rudimentary cavities and without a septum. There was an infundibular pulmonary stenosis, 0.9 cm. in circumference. The aortic valve measured 1.4 cms. in circumference and had three normal leaflets. The coronary arteries were normal.

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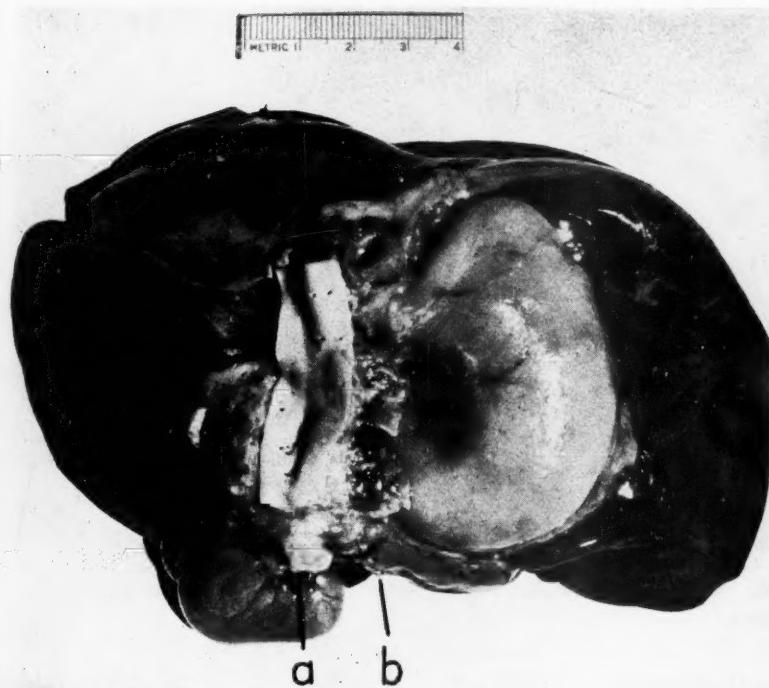


Fig. 19. Case 9. Symmetric liver, the left lobe equaling the right. The stomach is dextroposed. At (a), see accessory liver; at (b), see tip of the gall bladder. Along the greater curvature of the stomach, extending to (a), is the pancreas.

Anatomic diagnoses. Cor triloculare biventriculum; levocardia; foramen ovale, widely patent; tricuspid, common A-V valve; pulmonary stenosis, infundibular; symmetric liver; dextroposition of stomach; absence of gall bladder; agenesis of the spleen.

Case 9

J.C. (C.H. A-53-267). 4-month-old male with cyanosis since birth. The cyanosis persisted and the patient was admitted for evaluation of its cause. During hospital stay the cyanosis increased and the patient expired at the age of 4 months.

Clinical impression: Tetralogy of Fallot, extreme, with right aortic arch.

Autopsy. Peritoneal cavity. The liver was symmetric, with the gall bladder

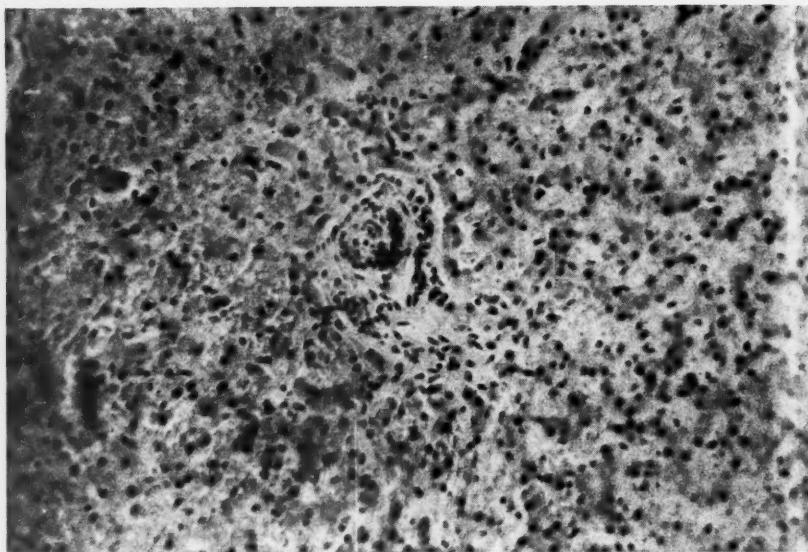


Fig. 20. Case 9. Section of accessory liver, thought on gross examination to be a spleen. x136.

in the right lobe. The stomach was transposed to the right upper quadrant, as was the pancreas. There was an accessory liver, measuring a few millimeters in diameter, attached to the posterior aspect of the duodenum on the right side, and adjacent to the gall bladder (Fig. 19). This accessory liver was misinterpreted, on gross examination, as a transposed rudimentary spleen. Histologically (Fig. 20), however, it consisted of liver tissue. There was a common mesentery running from the upper right to the lower left quadrant. *Heart, lungs and great vessels.* There was levocardia. The lungs had three lobes each. The inferior and superior venae cavae and the coronary sinus entered the right atrium; the pulmonary veins, the left atrium. There was pulmonary atresia with a transposed thread-like remnant of the pulmonary trunk ending blindly in the myocardium and situated to the left of the aorta (Fig. 21). There was a right aortic arch and a patent left ductus arteriosus. The right atrium was dilated. The interatrial septum showed a fenestration with four holes in the area of the foramen ovale, and a large defect in the lower anterior portion constituting an ostium primum. The interatrial septum arched over a common atrio-ventricular ostium that was guarded by four cusps without clefts. The cusps were confluent

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Fig. 21. Case 9. The heart, presenting the lower left ventricle and the upper portion of the right ventricle with the transposed aorta. The atretic pulmonary trunk is seen to the right of the aorta. There is a left ductus arteriosus arching over the right pulmonary artery to connect with the left pulmonary artery. The large interventricular septal defect is clearly seen.

through an interventricular septal defect encompassing the upper half of the septum. The cusps were attached to one group of papillary muscles on the lateral wall of each ventricle. From the anterior and upper aspect of the rudimentary interventricular septum, a 3 mm. thick muscular band coursed posteriorly and cephalad to insert to the left of and below the aortic outflow tract. This band traversed the ventricular cavity anteriorly to the anterior cusp of the common atrioventricular valve. The aorta

was transposed into the right ventricle; it showed three well formed leaflets and measured 3.0 cms. in circumference at the level of the valve. Two normal coronary arteries were found. In the thick wall of the right ventricle was a crista supraventricularis.

Anatomic diagnoses: Levocardia; persistent ostium primum; 4-cuspid common A-V valve; persistent foramen ovale with fenestrated valve; transposition of great arteries; pulmonary atresia; interventricular septal defect, membranous; patent ductus arteriosus; right aortic arch; symmetric liver; common mesentery; dextroposition of stomach and pancreas; accessory liver, rudimentary; agenesis of the spleen; trilobed lungs.

Case 12

D.L. (C.H. A-30—208). 9-month-old male born at full term after an uneventful pregnancy and delivery. At birth the color was dusky and, shortly afterwards, the infant developed intense cyanosis on crying. He had difficulties in feeding and often had upper respiratory infections. At the age of 3 months congenital heart disease was diagnosed. Frequent attacks of cyanosis developed and at the age of 9 months the child expired in respiratory distress.

Clinical impression: Congenital heart disease.

Autopsy. *Peritoneal cavity.* The larger lobe of the liver was in the left upper quadrant; the stomach was transposed to the right together with the pancreas. There was a common mesentery running from the right upper to the left lower quadrant and the cecum was in the upper right quadrant. There was no spleen. *Heart, lungs and great vessels.* There was levocardia. The lungs showed three lobes each. The inferior vena cava and a persistent left superior vena cava entered the left atrium. The right superior vena cava entered the right atrium. There was a right hepatic vein entering the right atrium. Only two pulmonary veins, one from each side, were present. They joined and were connected to the azygos vein that drained into the right superior vena cava. There was a left aortic arch with normal branching, except for the left vertebral artery that branched directly from the aorta as its third artery. The lungs received blood from two enlarged bronchial arteries emerging from the descending aorta. The hypoplastic pulmonary trunk ended blindly in the myocardium to the left of the aorta. Thus, there was pulmonary atresia. This pulmonary trunk's two main branches were hypoplastic, but contained lumens. No ductus arteriosus was present. The interatrial septum contained a widened foramen ovale measuring 0.4 cm. in diameter, and in addition there was a large defect in its lower anterior portion constituting an ostium primum. The

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interatrial septum arched over a common atrio-ventricular ostium guarded by two cusps and measuring 5.5 cms. in circumference. There was only a small posterior vestigial ridge constituting a rudimentary interventricular septum. The right part of the common ventricle had the configuration of a right ventricle. The aortic outlet had three normal leaflets and the coronary arteries were normal. The lungs showed bronchopneumonia and congestion. *Anatomic diagnoses:* Cor triloculare biventriculatum; levocardia; persistent ostium primum; widened foramen ovale, small; bicuspid common A-V ostium; transposition of the great arteries; pulmonary atresia; bronchial artery blood supply to lungs; anomalous pulmonary venous connection, complete, common pulmonary vein connected to azygous vein; anomalous systematic venous connections, partial, inferior and left superior venae cavae connected to left atrium; situs inversus of abdominal viscera; common mesentery; agenesis of spleen; trilobed lungs; bronchopneumonia, acute, hemorrhagic.

Case 13

J.E.N. (Karolinska Sjukhuset B.O. 15/51). 10-month-old white male with cyanosis since birth. There was slight dyspnea. Roentgenologic examination shortly before death revealed a picture suggestive of a Tetralogy of Fallot and a common mesentery.

Clinical impression: Tetralogy of Fallot.

Autopsy. Peritoneal cavity. Liver symmetric, the left lobe equaling the right in size. The stomach was transposed to the right. There was a common mesentery. The spleen was absent. *Heart, lungs and great vessels.* Levocardia. Lobation of lungs appeared normal. The inferior vena cava and a left superior vena cava entered the left atrium. The right superior vena cava and a hepatic vein entered the right atrium. The pulmonary veins were connected to the right superior vena cava without formation of a common trunk. The right superior vena cava was partially thrombosed. The valve of the foramen ovale was fenestrated. In the lower and anterior portion the interatrial septum showed an ostium primum, and the septum arched as a crescent over a common 4-cuspid atrio-ventricular ostium the cusps of which were irregular. There was an interventricular septal defect in the membranous portion, measuring approximately 1.5 cms. in diameter. The pulmonary trunk was transposed into the left ventricle, lying to the left of the aorta and markedly stenotic but not atretic, the stenosis being valvular. There was a left aortic arch, branching symmetrically, with two innominate arteries giving off their usual branches. The ductus arteriosus was closed. The coronary pattern was normal. In addition there was a left purulent otitis and a diffuse purulent meningitis.

Anatomic diagnoses: Levocardia; persistent ostium primum; fenestrated valve of the foramen ovale; 4-cuspid common A-V valve; transposition of the great arteries; pulmonary stenosis; interventricular septal defect, membranous; anomalous systemic venous connection, partial, persistent left superior vena cava and inferior vena cava connected to the left atrium; anomalous pulmonary venous connection, total, to right superior vena cava; otitis media, left; purulent meningitis; symmetric liver; dextroposition of stomach; common mesentery; agenesis of spleen.

Case 14

C.F. (C.H. A-41-173). $2\frac{1}{3}$ -year-old white female with dextrocardia and cyanotic heart disease diagnosed at the age of 2 months. She had episodes of intermittent cyanosis since early infancy and gradually developed clubbing. At the age of 2 years episodes of severe cyanosis, loss of speech, dyspnea and facial paralysis developed. During one of these attacks she expired at the age of $2\frac{1}{3}$ years.

Clinical impression: Congenital heart disease with dextrocardia.

Autopsy. Peritoneal cavity. The liver was symmetric with the gall bladder 2 cms. to the left of the midline. The stomach was in the upper right quadrant. There was a common mesentery; the descending colon, however, was fixed to the posterior abdominal wall. The head of the pancreas was normal; the tail was along the great curvature of the stomach. There was no spleen. *Heart, lungs and great vessels.* There was dextrocardia, the apex of the heart pointing to the right. The left lung had three lobes; the right lung, two. There was inversion of the sino-atrial region, the inferior and superior venae cavae entering the left-sided atrium, while the pulmonary veins entered the right atrium. The interatrial septum contained a large defect constituting $\frac{4}{5}$ of the entire septum in its lower anterior portion. The right atrio-ventricular ostium was bicuspid; the left, tricuspid. The aorta lay anteriorly and to the left of the pulmonary trunk that was transposed into the left-sided ventricle and was smaller than the aorta. The left-sided ventricle gave rise to the aorta and the pulmonary trunk and showed a well-developed crista supraventricularis. Thus, the ventricles were transposed. No arterial vessel emerged from the right-sided ventricle. There was a membranous interventricular septal defect measuring 1.5 cms. in diameter. The pulmonary outflow tract had two cusps and measured 0.9 cm. in diameter.

Anatomic diagnoses: Situs inversus of thoracic viscera with dextrocardia and inversion of sino-atrial region and transposition of ventricles; persistent

ostium primum; transposition of the great arteries; pulmonary stenosis, valvular; (partial transposition in dextrocardia with hypoplasia of pulmonary trunk, *Lev*, 1953 a); interventricular septal defect, membranous; symmetric liver; dextroposition of stomach and pancreas; common mesentery; agenesis of the spleen.

3. Type C

To this category three new cases belong: Nos. 5, 8, and 11.

Case 5

M.H. (C.H. A-53—243) 2-month-old white female with cyanosis and vomiting at birth. The cyanosis persisted and signs of paracolon meningitis were found. She recovered rapidly on antibiotics. As occasional vomiting persisted, a barium swallow was performed and malrotation of the bowel was found. The liver was enlarged. Occasional vomiting persisted, and during therapy she suddenly expired at the age of 2 months.

Clinical impression: Congenital heart disease.

Autopsy. *Peritoneal cavity.* There was symmetry of the liver. The gall bladder was in the right lobe of the liver. The stomach was on the right. There was complete malrotation of the bowel with a common mesentery. The spleen was absent. *Heart, lungs and great vessels.* There was levocardia. The inferior and superior venae cavae entered the right atrium and the pulmonary veins, the left atrium. The lower anterior portion of the interatrial septum showed a large defect representing a persistent ostium primum. The foramen ovale was widened. The right-sided atrio-ventricular valve was bicuspid, while the left-sided was tricuspid, malformed with tiny cusps, and was continuous with the right atrio-ventricular valve. There was a segmental transposition of the ventricles with a left-sided hypoplastic chamber communicating with the right-sided ventricle. The right-sided ventricle had the configuration of the normal left ventricle while the left-sided one had the configuration of a normal right ventricle with a crista supraventricularis. There was an interventricular septal defect in the membranous portion. There was transposition of the great arteries, the aorta arising from the left-sided (right) ventricle, and the pulmonary trunk, slightly wider than the aorta, from the right-sided (left) ventricle posteriorly and to the right of the aorta. The aorta branched normally. There was a patent left ductus arteriosus and a coarctation of the aorta between the left common carotid artery and the left subclavian artery. Thus, there was a partially corrected transposition of the great arteries.



Fig. 22. Case 5. The heart, with the left-sided (transposed right) ventricle opened to show the trabecular pattern of the transposed right ventricle. The persistent ostium primum is clearly seen in the center of the picture.

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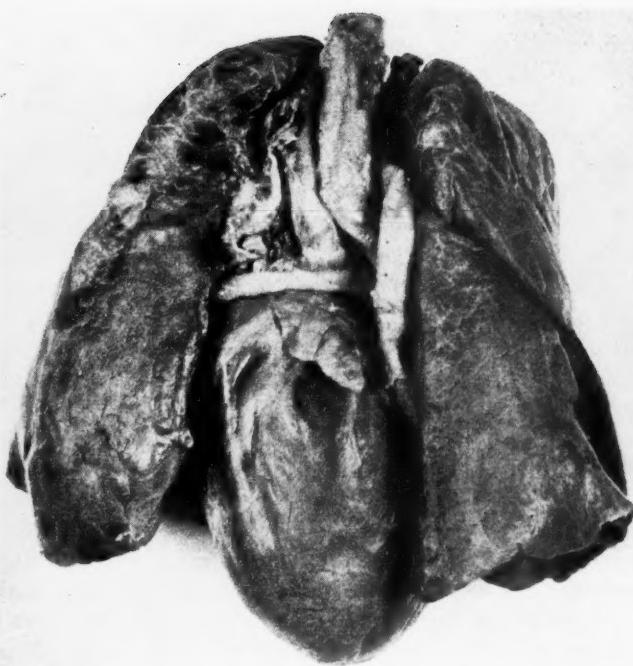


Fig. 23. Case 8. Heart-lung preparation, dorsal view. The pulmonary veins join to form a common channel seen to the left of the trachea. The aortic arch and the descending aorta are to the right of the trachea.

Anatomic diagnoses: Inversion of the sino-atrial region and segmental situs inversus of the ventricles; levocardia; persistent ostium primum; patent foramen ovale; right bicuspid and malformed left tricuspid A-V valves; complete transposition, partially corrected; interventricular septal defect, membranous; coarctation of the aorta; patent ductus arteriosus; malrotation of bowel, complete; absence of spleen; acute hemorrhagic bronchopneumonia; meningitis, healed.

Case 8

S.P. (C.H A-41-29). 4-month-old female born at full term. At the age of 2½ months she ceased to gain weight after an upper respiratory infection. At the age of 4 months she suddenly developed edema of the legs, cyanosis and dyspnea. The patient suddenly expired while in an oxygen tent.

Clinical impression: Congenital heart disease, type undetermined.

Autopsy. Peritoneal cavity. The liver was symmetric and the gall bladder was to the left of the midline. The stomach was in the left upper quadrant. There was a common mesentery and the cecum was found in the right upper quadrant. The spleen was absent. No right umbilical artery was found. *Heart, lungs and great vessels.* There was levocardia. The lungs showed abnormal lobation, the left having 4 and the right, 3 lobes. There was inversion of the sino-atrial region. The inferior vena cava and the coronary sinus entered the left atrium, and the superior vena cava, the right atrium. The left atrium contained a linea terminalis. All pulmonary veins joined and formed a common channel that was connected to the left innominate vein. This common channel was interpreted as a partially persistent left superior vena cava that had degenerated between the entrance of the pulmonary veins and the heart, thus acting as a "common pulmonary vein". The interatrial septum was deficient, the only remnant being a round median bar 1.5 cms. in length, tapering from a diameter of 0.6 to 0.3 cm. as it coursed from the postero-inferior to the antero-superior wall of the common atrium. There was a common atrio-ventricular ostium guarded by 4 cusps and measuring 2.5×3.0 cms. in greatest diameters. The ventricular septum was rudimentary and consisted of a vestigial rounded elevation in the lower anterior portion of the common ventricle. The aortic orifice was situated in front of and slightly to the right of the pulmonary outlet. It measured 0.9 cm. in diameter, while the pulmonary orifice measured 1.1 cms. in diameter. Both valves were furnished with three semilunar leaflets. There was a right aortic arch with branching the mirror image of normal. The ductus arteriosus was atretic. The coronary pattern was reversed. There were no signs of stenosis of the pulmonary orifice, neither infundibular nor valvular. *Anatomic diagnoses:* Cor biloculare; levocardia; 4-cuspid common A—V ostium; inversion of the sino-atrial region; transposition of the great arteries; right aortic arch; anomalous pulmonary venous connection, total, to partially persistent left superior vena cava ("common pulmonary vein") connected with left innominate vein; symmetric liver; common mesentery; agenesis of the spleen; abnormal lobation of lungs.

Case 11

L.S. (C.H. A-40-101). 6-month-old white male was delivered at full term and was not reported to have been cyanotic at that time. However, cyanosis gradually appeared, particularly after crying. On admission at the age of 6 months the heart and liver were enlarged. The child expired suddenly in circulatory collapse at the age of 6 months.

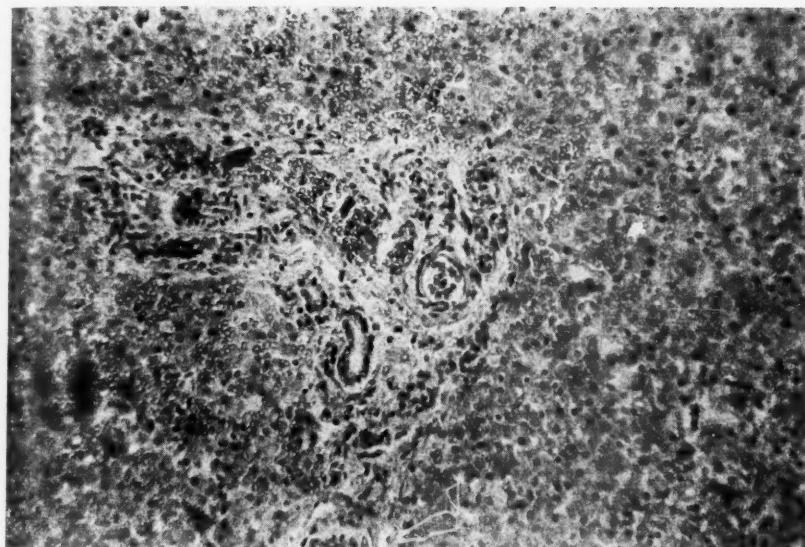


Fig. 24. Case 11. Section of accessory liver, thought on gross examination to be a spleen. $\times 136$.

Clinical impression: Congenital heart disease.

Autopsy. Peritoneal cavity. The liver was symmetric. The stomach was in the left upper quadrant. The head of the pancreas was normal, while the tail was bent forward and was located intraperitoneally between the stomach and the transverse colon. There was a common mesentery with the cecum lying in the midline. A small accessory liver measuring $3.0 \times 1.0 \times 0.1$ cms. was found to the left of the vertebral column, loosely attached to the liver. Grossly, this liver was interpreted as the spleen (cf. Case 9) but histologically it consisted of liver tissue (Fig. 24). *Heart, lungs and great vessels.* There was levocardia. The lungs had three lobes each. The inferior and superior venae cavae and the coronary sinus all entered the right atrium, as did two hepatic veins separately. There was completely anomalous venous connection inasmuch as the pulmonary veins joined the right subclavian and the right jugular veins to form the right innominate vein with drainage into the right atrium. The interatrial septum was deficient consisting of a falciform bar with a large interatrial septal defect in the upper, posterior portion and a widely patent ostium primum below. The interatrial septum arched over a common atrio-ventricular ostium guarded by four cusps without evidence

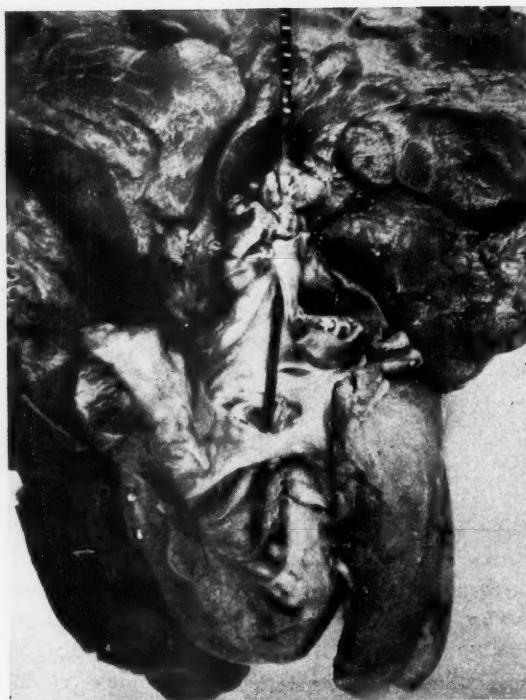


Fig. 25. Case 11. Cor biloculare. The only remnant of a septum is the falciform bar arching over the common A-V ostium. The primitive interatrial septum is seen in front of the probe.

of cleavage. The interventricular septum was absent and functionally the heart constituted a cor biloculare. The aorta arose to the right of and anteriorly to the pulmonary trunk, neither of these showing stenosis of the orifices. The ductus arteriosus was obliterated. The coronary pattern was normal.

Anatomic diagnoses: Cor biloculare; levocardia; 4-cuspid common A-V ostium; transposition of the great arteries; anomalous pulmonary venous connection, total, the pulmonary veins connected to the right jugular and right subclavian veins, forming the right innominate vein; symmetric liver; common mesentery; accessory liver, rudimentary; agenesis of the spleen; trilobed lungs; otitis media, left.

C. Survey of the Pathologic Features Displayed by Cases of Agenesis of the Spleen

It is evident from the preceding case reports and Tables A through D that there are considerable variations in the anatomic pattern of the material. Some main features that many cases have in common will be reviewed. Because of the method of selection, all show abnormalities of the heart as well as agenesis of the spleen. In addition, there are anomalies of the great arteries, as has been shown. A certain number show abnormal systemic and/or pulmonary venous connections. The lobation of the lungs is abnormal and the abdominal viscera often show varying degrees of situs inversus.

For details concerning the different anomalies, and for references, see Tables A—D at the end of the paper.

Dextrocardia

The definition by *Lichtman* (1931) is followed. Dextrocardia denotes a congenital condition in which the heart assumes a position in the right part of the thoracic cavity with the apex pointing to the right. No subdivision into *Lichtman's* three, or *Mandelstamm & Reinberg's* (1928) four, types has been attempted. Twenty-three cases display dextrocardia. Fifteen of these also show varying degrees of situs inversus.

Right aortic arch

If the arch of the aorta, or of a common truncus, crossed over the right bronchus it was designated as a right aortic arch. This was specifically stated in 25 cases; ten of these also showed dextrocardia.

Anomalies of the atrio-ventricular region

In 60 cases, descriptions of this region are available. Fifty-six cases showed an abnormal A—V region.

Most often there is a *common atrio-ventricular ostium*; 46 cases show this anomaly.

Fourteen of these are *four-cuspid* (*Krausse*, case 1, 1905; *Feldmann*, 1930; *Kugel*, 1932; *Rosman*, 1942; *Weinberg & Kolson*, 1949; *Author*, cases 1, 2, 4, 5, 6, 8, 9, 11, and 13).

Ten are *tricuspid* (*Arnold*, 1868; *Rokitansky*, 1875; *Epstein*, 1886; *Geipel*, 1899; *Shapiro*, 1930; *Leikin*, 1951; *Polhemus & Schafer*, cases 2, 3, and 4, 1952; *Author*, case 7).

Seven are *bicuspid* (*Gardère*, 1908; *Pernkopf*, case 4, 1926; *Hu*, 1929; *Campbell & Forgacs*, 1953; *Adler & van Slyke*, 1953; *Author*, cases 10 and 12).

Six are *five-cuspid* (*Behr*, 1932; *Fueter*, 1938; *Gerstenberger*, 1938; *Lighner*, 1939; *Durie & Wyndham*, case 2, 1942; *Conn et al.*, 1950).

Three had *one fused cusp* (*Lüdin*, 1952; *Baumann*, 2 cases, 1954).

One had *six cusps* (*Pernkopf*, case 5, 1926).

One had practically no valvular tissue (*Krausse*, case 2, 1905).

In the remaining four of the 46 cases with common A—V ostium, the number of cusps is not reported (*Taussig*, 1939; *Polhemus & Schafer*, case 1, 1952; *Campbell et al.*, case 6, 1953; *Willi & Gasser*, case 4, 1955).

Another type of malformation of the A—V region is *mitral atresia*, as inferred from the descriptions. This is present in five cases (*Lawrence & Nabarro*, 1901; *Mönckeberg*, 1915; *Kimura*, 1930; *Durie & Wyndham*, case 1, 1942; *Campbell et al.*, 1953).

Some of these cases have not been designated as cases of mitral atresia by the authors. The reasons for classifying them here, despite this fact, will follow. *Mönckeberg* (1915) does not use the term mitral atresia, but the case of that author is beyond doubt because of the thorough examination of the heart. Because of his complete examination, *Mönckeberg's* case deserves a special comment. It concerns a *cor biventriculum pseudotrilobulare* with rudimentary mitral valve and left ventricle visualized only after serial sectioning of the heart. *Mönckeberg* stresses the importance of histologic examination of congenitally deformed hearts, and considers this method of examination the only procedure for achieving an exact diagnosis in many cases of complicated congenital defects.

Kimura's case is not stated to be a case of mitral atresia in the original report. From the description of the heart this is not evident, and the description is incomplete. However, the pictures show the left atrium ending blindly towards the ventricle, and the right atrium seems to have been the only atrium in direct communication with the common ventricle. The atrio-ventricular valve is described as being irregular and furnished with several irregular valvular flaps. The A—V valve was malformed and in the inadequate description of the heart mitral atresia has not been ruled out. It seems very likely, as judged from the pictures. However, *Kimura* in his report focuses his main interest on associated genital anomalies. However the case of *Kimura* is classified, it displayed an anomalous atrio-ventricular valve.

Case 3 of *Campbell et al.* is not classified as an outright case of mitral atresia in their communication. To the present author it seems highly probable that it is, and it has been classified as such here, for the following reasons.

The left atrium was rudimentary; the right was very large. The left received the common pulmonary vein and did not open into the single ventricle. The left atrium communicated with the right by way of a slit-like defect of the lower anterior interatrial septum. There was a single tricuspid A-V valve. The authors point out that the left atrium was separated from the ventricle by ventricular myocardium and not by a thin membrane. The area of a possible, rudimentary left ventricle was not stated to be histologically examined. The single ventricle did not show any evidence of an interventricular septum. The great arterial trunks were transposed and emerged from this single (possibly right) ventricular cavity, the pulmonary trunk being stenosed. The possibility of a mitral atresia has not been ruled out.

A third type of anomalous A-V region is *tricuspid atresia*. This is highly probable in *Young's* (1947) case of a premature that had a diminutive right ventricle, absence of tricuspid valve, and a single atrium in communication with the left ventricle only by way of a bicuspid A-V valve. The aorta was transposed into the rudimentary right ventricle. The case of *Breschet* (1826), the original of which has not been accessible to the author, has also been included in this group. *Lichtman* (1931) states that the tricuspid is vestigial.

Two bicuspid A-V valves were present in two cases (*Gasser & Willi*, case 1, 1952; *Author*, case 3).

One of the author's cases showed *transposition of the A-V valves* in levocardia (case 14).

Thus, of the 60 cases with accessible descriptions of the atrio-ventricular region, four were reported as normal (*Birch-Hirschfeld*, 1871; *McLean & Craig*, 1922; and *Boggs & Reed*, 2 cases, 1953). As for *Boggs & Reed*'s two cases, they seem highly questionable as there is no detailed description of the area concerned, nor of the cardiac septa. Nevertheless, the authors state in their summary that "atrio-ventricularis communis" is one characteristic of the "syndrome" of splenic agenesis. It seems highly probable that there were anomalies in the A-V region, although it is passed over as "not unusual" in the description. *It is noteworthy that the two first-mentioned cases belonged to Type D and showed no truncus anomalies.*

The other two cases belonging to Type D include no accessible reports on the A-V region. *Bossert & Leichtentritt's* (1920) case report includes no mention of the atrio-ventricular valves, nor of the truncus region. *Valleis's* (1834) case is accessible to the author in *Putschar's* (1934) summary only. In this summary it is stated that there was a left tricuspid valve and situs inversus of the heart. The right atrio-ventricular valve is not mentioned, nor is the truncus region.

In summing up the findings of A—V anomalies with reference to the types of truncus malformations, the following is found.

Type A includes a total of ten cases. Nine of these showed A—V anomalies, and one (*Garvin*, 1927) included no description of the area concerned.

Type B comprises 41 cases. Thirty-six of these displayed A—V anomalies, two were reported normal (*Boggs & Reed*, 1953), and three case reports included no description of the A—V region (*Kundrat*, 1887; *Gasser & Willi*, case 2, 1952; *Bush & Ainger*, 1955).

Type C contains 14 cases. Eleven of these showed A—V anomalies, and in three no description was given of the region in question in available reports (*Martin*, 1826; *Kundrat*, 1888; *Jaccard*, 1951).

Type D, finally, consists of four cases, two of which were reported to be normal (*Birch-Hirschfeld*, 1871; *McLean & Craig*, 1922), and two of which did not contain any description of the A—V region (*Valleix* 1834; *Bossert & Leichtentritt*, 1920).

Anomalies of the cono-truncus region

These have been described in Part II, Section B. Suffice it here to emphasize that 65 cases out of 69 contained data to show that this region was anomalous. Two cases were reported normal (*Birch-Hirschfeld*, 1871; *McLean & Craig*, 1922); one contained no complete description (*Valleix*, 1834); and one did not mention the region in any way (*Bossert & Leichtentritt*, 1920).

Septal defects

Varying degrees of interatrial and/or interventricular septal defects are present in all cases except two with incomplete descriptions (*Kundrat*, quot. by *Schrötter*, 1887; *Kundrat*, 1888). The anatomic variation is wide. Thus, 32 cases are examples of *cor biloculare* with absence of septa, or with a small muscular band traversing the common atrium in a postero-inferior to antero-superior direction. Eighteen cases display an ovoid defect in the region of the *ostium primum* with an atrial septum arching over the atrioventricular ostium. There are no data concerning cleavage of the mitral leaflets. In the author's own material no case with cleft mitral valve is present; nor has it been possible to collect cases of agenesis of the spleen in case reports with true examples of this anomaly (e.g., *Rogers & Edwards*, 1948; *Curtin*, 1952; *Edwards*, 1953 a).

Occasionally, there are defects in the area of the *foramen ovale*. Ten cases with this anomaly have been collected. Among these, *Birch-Hirschfeld's* (1871) case deserves a note. *Putschar* (1934) classifies that case in a group

without cardiac anomalies. However, as *Putschar* points out, there was a more than 2-groschen large "foramen ovale" in the atrial septum. The case concerned a new-born (age "several hours", no birth-weight given) that died suddenly. As the only unusual finding in the heart, *Birch-Hirschfeld* found this more than 2-groschen large "foramen ovale". A 2-groschen ("2 Neugroschen") from Sachsen, Germany, of 1868 has a diameter of 21 mms. (*Rasmussen*, 1955). Suffice it to say that an interatrial septal defect measuring approximately 20 mms. in diameter in infancy can hardly be classified as a "foramen ovale". *Birch-Hirschfeld* points out that he was unable to close the defect by pressing the valve of the foramen ovale against the atrial septum. However, the author did not mention whether the atrial septum was deficient in its anterior lower portion; so the defect cannot be classified as a true ostium primum.

Anomalous connections of pulmonary veins

This term covers anatomic conditions in which pulmonary veins terminate in any vessel or chamber other than the left atrium (*Edwards*, 1953 b). It is to be distinguished from *anomalous drainage* which denotes abnormal blood flow from the lungs with or without abnormal termination of pulmonary veins (*Edwards, DuShane, Alcott & Burchell*, 1951; *Swan, Burchell & Wood*, 1953; *Edwards*, 1953 b). The connections can be partially or totally abnormal.

Totally anomalous pulmonary venous connections were found in 31 of the 69 cases presented. Most commonly, the pulmonary veins joined the right superior vena cava. This occurred in 12 instances (*Epstein*, 1886; *Geipel*, 1899; *Mönckeberg*, 1915; *Garvin*, 1927; *Durie & Wyndham*, case 1, 1942; *Boggs & Reed*, case 1, 1953; *Baumann*, 2 cases, 1954; *Willi & Gasser*, case 4, 1955; *Author*, cases 4, 12 and 13). In one of these the pulmonary veins drained into the azygos vein and then into the right superior vena cava (*Author*, case 12). In three other cases the veins first joined the innominate vein before draining into the right superior vena cava (*Gasser & Willi*, case 2, 1952; *Author*, cases 8 and 11). In the writer's Case 8 (Fig. 23) and in Case 2 of *Gasser & Willi* (1952) there was a "common pulmonary vein" connected with the left innominate vein. It was interpreted as a partially persistent left superior vena cava (see below, Anomalous connections of systemic veins, p. 62). In seven instances the pulmonary veins terminated in the right atrium (*Rokitansky*, 1875; *Krausse*, case 2, 1905; *McLean & Craig*, 1922; *Pernkopf*, case 4, 1926; *Leikin*, 1951; *Bush & Ainger*, 1955; *Author*, case 14). In no less than seven cases, a common pulmonary vein joined

the portal vein (*Arnold*, 1868; *Hu*, 1929; *Young*, 1947; *Weinberg & Kolson*, 1949; *Jaccard*, 1951; *Lüdin*, 1952; *Author*, case 6). In one case (*Boggs & Reed*, case 2, 1953) the pulmonary veins joined different systematic veins (right superior vena cava, left innominate and inferior vena cava) before draining eventually into the right atrium.

One example of *totally anomalous pulmonary venous connection with normal drainage* was found in the literature (*Gerstenberger*, 1938). This case is principally similar to that of *Becu, Tauxe, DuSchane & Edwards* (1955) with a suggestion of a *cor triatriatum*. A small sinus was formed by the joined left superior vena cava and a common pulmonary vein. The common pulmonary vein was collecting all pulmonary veins, and the sinus opened into the left atrium. In other words, the pulmonary veins were abnormally connected with a persistent left superior vena cava. As this vein terminated in the left atrium without any connection with the coronary sinus, the *drainage* was normal.

Partially anomalous pulmonary venous connections were present in five cases (*Kimura*, 1930; *Lightner*, 1939; *Author*, cases 1, 3 and 10). In every instance the anomalous connection concerned the right pulmonary veins that were connected with the right atrium. In all these cases the left pulmonary veins terminated in the left atrium; so there were symmetrically abnormal connections.

Another form of anomalous pulmonary venous connection is the *common pulmonary vein*. This denotes conditions in which pulmonary veins form a common channel. This is the case in all instances mentioned above where there was abnormal connection with the portal vein. Occasionally, a common pulmonary vein empties into the left atrium. A common pulmonary vein was present in 20 cases, in five of which it was connected with the left atrium. In each of five cases it was connected with the right superior vena cava; in seven with the portal vein; in two cases with the right atrium and in another case with the azygos vein. In Case 2 of *Boggs & Reed* (1953) a common pulmonary vein was formed by the veins of the lower lobes only. This common vein was connected with the inferior vena cava.

Anomalous connections of systemic veins

This is present in 29 instances. In addition, there are two probable cases (*Feldmann*, 1930; *Jaccard*, 1951). *Feldmann* states that the left superior vena cava emptied into the left ventricle (sic!). In *Jaccard's* case there were bilateral superior venae cavae and a common atrium, but the author does not state which part of the atrium received the left superior vena cava.

Most commonly, there is partially anomalous connection in the form of a *left superior vena cava* connected with the *left atrium*. This was the case in 27 instances, including the cases of *Feldmann*, *Jaccard*, and *five cases with inversion of the sino-atrial region* (*Arnold*, 1868; *McLean & Craig*, 1922; *Pernkopf*, case 4, 1926; *Bush & Ainger*, 1955; *Author*, case 14). In no instance is the left superior vena cava reported as draining into the coronary sinus, as is otherwise commonly the situation when this vein persists into postfetal life (Group I (A) of *McManus*, 1941; *Edwards*, 1953 a). In 19 cases there were a right and a *persistent left superior vena cava*, symmetrically connected with the right and left atria, respectively. *McManus'* (1941) classification of the various types of left superior vena cava does not include conditions in which the vein is connected with the left atrium. To the writer the term *persistent* should be reserved for cases where there are bilateral venae cavae. Thus, the following classification is proposed:

- I. Persistent left superior vena cava,
 - A) Connected with the coronary sinus
 - B) Connected with the pulmonary veins (partially persistent left superior vena cava)
 - C) Connected with the left atrium
- II. Left superior vena cava without right superior vena cava.

The term *persistent left superior vena cava* is retained as it is in common use. Embryologically, the correct term would be *persistent left anterior cardinal vein*. This classification is a modification of that of *McManus* (1941), with the addition of Group I (C) which is represented by 19 cases in the present material.

In the above-mentioned cases with inversion of the sino-atrial region, the *Author's* Case 8 is not included. There was a "common pulmonary vein" connected with the left innominate vein, and the anomaly is an example of Group I (B) in the above classification. It is in this respect similar to Case 4 of *Gardner & Oram* (1953). Case 2 of *Gasser & Willi* (1922) shows the same type of anomaly.

Among the 31 cases with anomalous connection of systemic veins (including the cases of *Feldmann* and *Jaccard*) there are nine cases described as having hepatic veins, separately connected with the atrium which did not receive the inferior vena cava. Of these, three had no left superior vena cava (*Rokitansky*, 1875; *Epstein*, 1886; *Young*, 1947) and have not been accounted for in the above description. The hepatic veins connected separately with the atria are interpreted as *persistent omphalomesenteric veins* (*venae revehentes hepatis*; *Mall*, 1906; *Broman*, 1921; *Mönckeberg*, 1924).

Three cases had an inferior vena cava connected with the right atrium (*Martin*, 1826; *Rokitansky*, 1875; *Epstein*, 1886), and a hepatic vein connected with the left atrium. This hepatic vein represents a *persistent left omphalomesenteric vein*. In six cases the inferior vena cava was connected with the left atrium (*Mönckeberg*, 1915; *Fueter*, 1936; *Young*, 1947; *Leikin*, 1951; *Author*, cases 12 and 13). The right hepatic vein connected with the right atrium in these cases is interpreted as a *persistent right omphalomesenteric vein*. *Bush & Ainger's* case (with inversion of the sino-atrial region) is a probable seventh case with persistence of the right omphalomesenteric vein. Anglo-cardiography showed that case to have "bilateral inferior vanae cavae". This possibility is, however, not stated to be confirmed in the autopsy report.

The above-mentioned seven cases with a common pulmonary vein connected with the portal vein may be interpreted as showing persistence of an omphalomesenteric vein, as pointed out by *Weinberg & Kolson* (1949) and in *Jaccard's* (1951) paper.

In addition, there are other anomalies of the systematic veins such as *absent coronary sinus* (e.g., *Pernkopf's* 2 cases, 1926) and a left azygos vein connected with the left superior vena cava (e.g., *Durie & Wyndham*, case 2, 1942).

Abnormal lobation of lungs

This is found in 46 cases. Most commonly, there is symmetric lobation, the lungs being mirror images of each other. This is the case in 40 instances. Most often, there are three more or less complete lobes in each lung. Thirty-five cases show trilobed and four, four-lobed lungs, while in one case the lungs were five-lobed.

Anomalous abdominal viscera

By definition, the spleen is absent in all cases. The liver is often transposed to the left side, the larger lobe being situated in the left upper quadrant (17 cases); or it is symmetric, the left lobe equaling the right in size (31 cases). The stomach is transposed to the right upper quadrant in 33 cases. There is a common mesentery, more or less complete in 33 cases. In addition, there are minor anomalies of the pancreas (annular; tail transposed, etc.). In summary, the abdominal viscera show varying degrees of situs inversus with a tendency towards symmetry, most marked in the shape of the liver and in the attachment of the mesentery.

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A note on symmetry

It is evident from the preceding descriptions of cases of cardiac malformations associated with agenesis of the spleen that the varied picture of malformations has a common pattern with a tendency towards visceral symmetry.

Thus, the *great arteries* display symmetric features. There are varying degrees of symmetric arrangement of the truncus derivatives: truncus communis, pulmonary atresia, and transposition of the arterial trunks. There is one case interpreted as persistence of double ductus arteriosus (*Author*, case 2).

The *systemic veins* may display symmetry, most often in the form of a persistent left superior vena cava, and occasionally, persistence of omphalo-mesenteric veins occurs.

The *pulmonary veins* likewise may have a symmetric pattern, with persistence of a common pulmonary vein or with the left pulmonary veins connected with the left, and the right, with the right atrium.

The *heart* may display a pattern that could be interpreted as symmetric; cor biloculare with complete absence of cardiac septa is a common finding in this "syndrome of visceral symmetry".

The *abdominal organs* display symmetric arrangement in a number of cases. The liver often has a left lobe equaling the right in size and shape. There is a common mesentery in a number of cases. As has been repeatedly stressed in the literature, partial or total situs inversus is part and parcel of this tendency to symmetry (e.g., *Toldt*, 1889; *Geipel*, 1899 and 1903; *Tondury*, 1936; *Torgersen*, 1949, 1950 a and 1950 b). It is not the intention of the author to discuss the varying forms of symmetry or situs inversus that have been shown to occur in these cases (cf. *Harrison*, 1945; *Torgersen*, 1949 and 1950 b). It would be beyond the scope of this paper.

The author suggests that this syndrome should be called asplenia, a teratologic syndrome of visceral symmetry. This is in analogy with the teratologic syndromes produced by vitamin A deficiency during gestation (*Wilson* & *Warkany*, 1950 and 1953; *Warkany*, 1952/53).

On the occurrence of serious infections

Agenesis of the spleen in infancy and childhood is usually associated with severe malformations of the heart and great vessels, as is evident from this survey. Eleven cases out of the 12 with agenesis of the spleen in an autopsy series comprising 7,032 infants and children, showed associated malformations of the heart and great vessels. The twelfth case, a 9-month-old white female,

(C.H., A-25—167), showed purulent meningitis without associated anomalies of the cardiovascular system. For the latter reason, it has not been included in this study. It is mentioned in this context, however, as *King & Shumacker* (1952) have called attention to the relative frequency of infections, meningitis in particular, following splenectomy in infancy. These authors collected 15 cases in which splenectomy had been performed before the age of six months. Of these, six contracted serious infections, and three of them died. Among these, *King & Shumacker* report four cases with either meningitis or overwhelming meningococcemia. *Gross* (1953) does not have the same experience. After 58 successful splenectomies performed on children, there have been only two known deaths from severe infections, one of these being meningitis. *Gellis* (1954), in a comment on *Boggs & Reed's* abstracted paper, points out that he has encountered three cases where septicemia developed several months after splenectomy.

In the material presented here, 11 cases showed evidence of serious infections at the time of death. Of these, four had *meningitis* (*Bossert & Leichtentritt*, 1920; *Polhemus & Schafer*, case 3, 1952; *Author*, cases 5 and 13). One had ulcerative *endocarditis* of a bicuspid pulmonary valve and abscesses in the kidneys (*Gardère*, 1908). Five showed *bronchopneumonia* (*Gardère*, 1908; *McLean & Craig*, 1922; *Author*, cases 5, 6 and 12). Three had *otitis media* (*Author*, cases 3, 11 and 13). One had pulmonary *tuberculosis* (*Shapiro*, 1930). This incidence of infections is not significantly higher than that of *Abbott's* (1936) even if only her cases of bacterial endocarditis and bronchopneumonia are counted, and not including the ill-defined group of "cerebral causes of death" in which bacterial infections are not listed separately from other diseases.

Five cases of meningitis occurred in 66 cases of asplenia, including the above-mentioned case without cardiovascular malformations (A-25—167), but excluding two stillbirths (*Young*, 1947; *Author*, case 1) and two cases in which examination of the cranial contents was not permitted (*Boggs & Reed*, 2 cases, 1953). This incidence might seem to support the findings of *King & Shumacker* (1952). They emphasize that splenectomy performed before the age of six months may cause meningitis in a higher proportion than when it is carried out later. In the material presented here all cases of meningitis died at or before the age of 10 months. The similarity between this material and that presented by *King & Shumacker* may only be apparent, however, as both series are very small. As mentioned, the occurrence of infections in the present material is not significantly higher than in that of *Abbott*. Besides, another series of splenectomies carried out in infancy does not tend to support the findings of *King & Shumacker*. Thus, in the Boston Children's

Medical Center material of 18 instances of splenectomy on infants below the age of one year, only two developed meningitis (*Howell*, 1955). These two cases had been splenectomized because of congenital thrombocytopenic purpura.

Boesen & Vendel (1955 a) found four instances of meningitis in an autopsy series from Scandinavia comprising 1,137 cases of congenital heart disease in children under four years of age. None of these four cases was associated with asplenia. There were five cases of asplenia in that material, none of which was reported to have developed meningitis. Ninety per cent of these 1,137 cases died before the age of one year (*Boesen & Vendel*, 1955 b).

In view of the evidence presented, the findings of four cases of meningitis in the material of cardiovascular malformations presented by the author cannot be said to support the view of *King & Shumacker* (1952) that the spleen *per se* should be of particular value in combating infections during infancy. *Howell* (1955) mentions the possibility that the occurrence of meningitis after splenectomy might be due to the underlying error that was the reason for splenectomy, as, for example, congenital thrombocytopenic purpura.

PART III

Congenital Malformations of the Heart and Great Vessels Associated with Splenic Anomalies other than Agenesis

Occasionally, cardiac defects are encountered in cases with hypoplastic spleens, and also in cases with multiple spleens. The cardiac malformations of these cases have many features in common with those lacking spleens. These cases will not be treated extensively in this paper. This has been avoided for several reasons. First, there is considerable difficulty in defining the terms hypoplasia and multiple spleens. Hypoplasia of the spleen may result as a sequela of disease other than maldevelopment. Multiple spleens are often encountered in the form of splenunculi associated with a main spleen. Second, the purpose of this paper is to study cardiac defects, the basic lesions of which appeared at approximately the same time during organogenesis. The absence of the spleen is taken to indicate that this time coincided with the early formative phase of development of that organ. Including any other type of malformed spleen would invite several sources of error in that assumption. It might seem reasonable to assume that organogenesis of the spleen went astray somewhat later in cases of hypoplasia or duplication of the organ. Taking this for granted, however, would be fallacious.

To substantiate the above statements, four cases of cardiac defects with malformed spleens will be described, with short comments added.

An example of hypoplasia of the spleen associated with congenital heart disease

Case 15

T.P.C. (C.H. A-51-287). 6-day-old white male, born 2 weeks prematurely. Three hours after birth he became cyanotic. Apneic periods developed gradually. During one of these spells the patient expired.

Autopsy. Peritoneal cavity. The liver was symmetric, with the gall bladder in the midline. The stomach was dextroposited. The appendix was in the left iliac fossa. There was a common mesentery. The great omentum was absent. The spleen (Fig. 26) was found behind the stomach in the right valve;

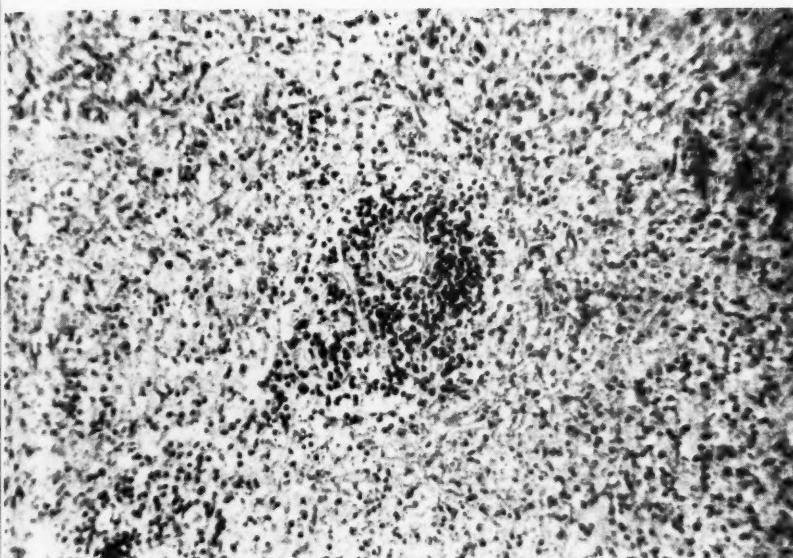


Fig. 26. Case 15. Section of hypoplastic spleen, with a small Malpighian follicle. x136.

hypochondrium and weighed 3 grams. The adrenals were fused in the midline. *Heart, lungs and great vessels.* There was levocardia. The right lung had three lobes, the left two. The inferior and superior venae cavae were connected with the right atrium. There was no left superior vena cava. There was completely anomalous pulmonary venous connection; a common pulmonary vein was connected with the innominate vein. This common pulmonary vein was interpreted as a partially persistent left superior vena cava. There was a 0.5 cm. interatrial septal defect without a valve in the area of the foramen ovale. There was an interventricular septal defect measuring 2×4.5 cms., the septum being reduced to a narrow wedge. There were four atrio-ventricular cusps, the anterior mitral being fused with the anterior tricuspid through the interventricular septal defect. The pulmonary orifice was atretic. The pulmonary trunk lay behind and to the left of the aorta. The aortic orifice had three well-formed leaflets and measured 4 cms. in circumference. There was a left aortic arch with normal branching. The ductus arteriosus was patent. The coronary artery pattern was unremarkable.

Anatomic diagnoses: Cor biventriculare triloculare; levocardia; 4-cuspid A—V valve; pulmonary atresia with transposition of the great arteries; patent

ductus arteriosus; anomalous pulmonary venous connection, complete, common pulmonary vein (question of partially persistent superior vena cava) connected with the innominate vein; interatrial septal defect; symmetric liver; common mesentery; dextroposition of stomach; hypoplasia of spleen, with weight of 3 grams (normal equals 9 grams).

Comment. Case 15 displays anomalies of the cono-truncus that would qualify the case for placement in Type B: pulmonary atresia with transposition. There was an anomalous A-V valve with four cusps. The symmetric arrangement of the superior vena cavae, the liver and the mesentery is evident. The septal defects and the common pulmonary vein are further characteristics that are encountered in cases of agenesis of the spleen. In short, the anomalies are indistinguishable from those of splenic agenesis belonging to Type B, save for the hypoplasia of the spleen. That organ was examined histologically and consisted of splenic tissue (Fig. 26).

Two examples of double spleen associated with congenital heart disease

Case 16

L.C. (C.H. A-41-26). 10-day-old female, not reported to have been cyanotic at birth. At 2 days of age she began to vomit. An exploratory laparotomy was performed, and intestinal obstruction was found. After lysis of adhesions, the course went down-hill with evidence of persistent obstruction. Death occurred at 10 days of age.

Autopsy. Peritoneal cavity. Liver, symmetric. Stomach, transposed to the right. Two spleens anterior to the great curvature of the stomach measured $2.5 \times 1.4 \times 1.0$ and $1.6 \times 1.0 \times 0.7$ cms., respectively. The former had five distinct lobules and was situated superiorly to the latter. There was a diffuse peritonitis. Heart, lungs, and great vessels. There was levocardia. The right lung had two lobes and the left was incompletely divided into a third upper lobe. There was inversion of the sino-atrial region. All systemic veins were connected with the left atrium; there were bilateral superior vena cavae. The right connected with the coronary sinus that drained into the left atrium. The right pulmonary veins were connected with the right atrium, the left with the left atrium. The right atrium was about $1/4$ the size of the left. There was fenestration of the fossa ovalis, the valve leaflet of which was situated on the right side of the septum. The A-V valves were unremarkable. The aortic orifice equaled the pulmonary in diameter and there was no transposition of the great arteries. There was a left aortic arch with normal branching. The coronary pattern was not unusual. The azygos vein was on the left and drained into the left superior vena cava.

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There was a hemiazygos vein that drained into the right superior vena cava. The azygos and hemiazygos veins were interpreted as being persistent post-cardinal veins. There was no innominate vein.

Anatomic diagnoses: Levocardia; inversion of sino-atrial region and its connections; anomalous pulmonary venous connections, partial; right pulmonary veins connected with the right atrium and left pulmonary veins with the left atrium; anomalous systemic venous connection, total, all systemic veins connected with the left atrium (RSVC by way of coronary sinus); azygos vein connected with left superior vena cava; hemiazygos vein connected with right superior vena cava; fenestration of fossa ovalis; symmetric liver; dextroposition of stomach; dextroposed double spleen; peritonitis, postoperative, (intestinal obstruction, neonatal, postoperative).

Comment. Case 16 had two dextroposed spleens, one of which was divided into five lobules. No anomalies were found in the cono-truncus region, nor of the atrio-ventricular valves. The anomalies were limited to the venous connections, with inversion of the sino-atrial region. This case is somewhat different from the cases without spleen. A persistent right superior vena cava connected with the coronary sinus draining into the left atrium is not encountered in any of those cases. It is interesting to note the normal cono-truncus and A-V regions.

Case 17

G.M. (C.H. A-51-173). 7½-month-old white male. Cyanosis developed shortly after birth. Cyanosis was more prominent on crying. Cyanosis gradually increased and daily attacks appeared. During one of these spells the patient expired at the age of 7½ months.

Autopsy. Peritoneal cavity. The liver was symmetric and the gall bladder was in the midline. The stomach was on the left. There was a common mesentery. Two spleens were found to the left of the gastro-colic ligament. They measured $3.5 \times 1.5 \times 1.0$ and $1.7 \times 1.7 \times 1.5$ cms., respectively. *Heart, lungs and great vessels.* Levocardia, lobation of lungs unremarkable. The inferior vena cava entered the right atrium, as did the right superior and the persistent left superior vena cava. The latter entered the atrium by way of the coronary sinus. The two pulmonary veins, one from each lung, joined to form a common pulmonary vein that was connected with the right superior vena cava. There was a patent foramen ovale opening into a left rudimentary atrium into which no vessels emptied. The mitral orifice was atretic. The interventricular septum was absent and no rudimentary left ventricle could be found. The right atrium entered the common

ventricle through a tricuspid valve measuring 3.5 cms. in circumference. The aorta arose anteriorly and to the right of the pulmonary trunk. The pulmonary orifice showed a valvular and an infundibular stenosis. The pulmonary valve had three leaflets. The pulmonary trunk measured 0.8 cm. in circumference, the orifice 0.5 cm. in circumference; i.e., there was a post-stenotic dilatation. No ductus was found. There was a right aortic arch with branching that was a mirror image of the normal. The coronary arteries were not unusual.

Anatomic diagnoses: Cor triatriatum triloculare; levocardia; mitral atresia; transposition of the aorta with pulmonary stenoses, valvular and infundibular; anomalous pulmonary venous connection, total, with right superior vena cava; persistent left superior vena cava draining into coronary sinus; right aortic arch; symmetric liver; common mesentery; double spleen.

Comment. Case 17 had two spleens. There were mitral atresia and pulmonary stenosis with transposition of the great arteries. It would fit into Type B, like Case 15. The abnormal cono-truncus is associated with an anomalous A—V region.

An example of tripartite spleen associated with congenital heart disease

Case 18

M.A.P. (C.H. A-51-32). 4-month-old white female with cyanosis at birth. Gradually the patient went into respiratory distress, and cyanosis increased. She expired at the age of 4 months.

Autopsy. Peritoneal cavity. All the abdominal organs were normally situated. There were three spleens, measuring from 1 to 3 cms. in greatest diameters and weighing 18 grams together. They were found in the left upper quadrant behind the stomach. *Heart, lungs and great vessels.* Levocardia. Normal lobation of lungs. The systemic veins were connected with the right atrium, the pulmonary veins, with the left, as normally. The foramen ovale was patent and measured 0.2 cm. in diameter. The atrio-ventricular valves were unremarkable. There was a membranous interventricular septal defect measuring 0.5 cm. in diameter. The aorta was approximately 50 per cent dextroposed, overriding the interventricular septal defect. The aortic valves were not unusual. There was a right aortic arch. The pulmonary orifice was stenotic, and the leaflets were malformed and composed of small irregular thickenings of the endocardium at the circumference of the valvular ring. There was a post-stenotic dilatation of the pulmonary trunk, measuring 2.4 cms. in circumference just above the valvular ring. The right ventricle appeared normal.

Anatomic diagnoses: Levocardia; tetralogy of Fallot; dextroposition of aorta; pulmonary stenosis, valvular; right aortic arch; hypertrophy of right ventricle; patent foramen ovale; interventricular septal defect, membranous; three spleens.

Comment. Case 18 had three spleens, together weighing 18 grams (normal at this age, 16 grams). There were anomalies of the cono-truncus to qualify this case for placement in Type B, pulmonary stenosis with transposition. No A-V anomalies were found. This case is an example of abnormal cono-truncus without A-V anomalies.

As mentioned by *Putschar* (1934), cases with multiple spleens may occur with or without congenital heart disease. That author gives several examples from the literature showing that congenital heart malformation is not a constant feature of cases with multiple spleens. *Putschar* mentions 14 cases with double spleen two of which had associated heart malformations, and 16 cases with multiple spleens six of which were associated with congenital heart disease. *Putschar* briefly reviews several cases of multiple spleens where the heart is not mentioned.

To illustrate the occurrence of multiple spleens without cardiac malformation the following example is given.

An example of multiple spleens without associated congenital heart malformation

Case 19

S.McG. (C.H. A-43-197). A 1-year-old white female expired with signs of fulminating infection 12 hours after admission to an outside hospital.

Autopsy. Peritoneal cavity. The right lobe of the liver was greater than the left. The gall bladder was in the midline. The stomach was dextroposed and the great curvature reached the lateral abdominal wall in the right anterior axillary line. The pylorus was situated immediately below and slightly to the right of the gall bladder. Included in the posterior attachment of the stomach and against the posterior abdominal wall there was a series of small spleens. The lowest measured $0.5 \times 0.5 \times 0.5$ cm. Above this one there were two approximated spleens measuring respectively $2 \times 1.2 \times 1.5$ cms. and $2.2 \times 1.8 \times 1.6$ cms. Three more accessory spleens were found more anteriorly, measuring $0.6 \times 0.6 \times 0.6$ cm., $0.3 \times 0.2 \times 0.1$ cm., and $0.1 \times 0.1 \times 0.1$ cm. There was only one umbilical artery. The entire colon was intraperitoneal and there was a common mesentery. The cecum was in the left fossa ilica. *Heart and great vessels.* There was levocardia. The great veins were moderately distended but showed the normal anatomic features. The superior and inferior vena cavae and the coronary sinus

entered the right atrium; and the pulmonary veins, the left. The foramen ovale was probe-patent. There was no interventricular septal defect. The great arteries were normal. The valve and wall measurements of the heart were: A.V., 2.9; P.V., 3.2; M.V., 3.5; T.V., 4; L.V.M., 0.9 and R.V.M., 0.5 cms. The coronary arteries were normal.

Final diagnosis: Unexpected death; pneumococcus Type VI bacteremia; mal-rotation of gastro- intestinal tract; dextroposition of stomach and pancreas; multiple spleens.

Comment. This is a case where 6 spleens were found but no signs of congenital heart malformation. There was evidence of partial abdominal situs inversus with dextroposition of stomach and pancreas and a common mesentery, features that *Putschar* considers to be common in these cases.

Discussion

As can be seen from these case reports and the examples from the literature to follow, there are great similarities, except for Case 19, between these cases and those with absence of spleen; but the anatomic variation in the cases just presented is still wider than in cases with splenic agenesis. Because of their similarity, they have been mentioned in this part. Because of the proportionally wide anatomic variation and because congenital heart disease is not as constant a feature in these cases they will not be included in the material of absent spleens.

In the literature, several cases similar to those outlined in this part are found. Reference may be made to the following examples, chosen at random, and encountered in the literature during search for cases without spleens.

Lochte (1898) found two dextroposed spleens in a case of transposition of the great arteries with pulmonary stenosis and transposed A—V valves in levocardia. The tricuspid valve was irregular and malformed. There were anomalous systemic and pulmonary venous connections.

Geipel (1903, Case 1) describes a case of dextrocardia with transposition of the great arteries, single bicuspid A—V valve and six separate, equal-sized small spleens.

Royer & Wilson (1908) report a case with five dextroposed spleens, levocardia, transposition of the great arteries, malformed A—V valves, septal defects, and symmetric liver.

Miller (1925) describes a case with six small, dextroposed spleens. There were levocardia, transposition of the great arteries, fused A—V valves, septal defects, anomalous venous connections, and trilobed lungs.

A rudimentary spleen is described in the paper by *Doliopoulos & Maillet* (1952). It concerns a 4-year-old female who expired on the operating table during preparations for a shunt operation. Autopsy revealed pulmonary atresia with transposition of the great arteries, patent ductus arteriosus, single A-V valve and single ventricle. A "rudimentary spleen" was situated in the right hypochondrium ("la rate rudimentaire se trouve à droite"). No weight or size of the organ was recorded, nor was it stated to have been examined histologically. This case is noteworthy, considering the fact that, grossly, an accessory liver might easily be mistaken for a spleen. This mistake was made in gross examination of two of the present author's cases (Case 9, Type B; Case 11, Type C). Not until the alleged spleens in these cases were examined histologically was their true nature of accessory livers ascertained (Figs. 20 and 24). However, as Case 15 shows the similarity of the associated anomalies in a case of hypoplastic spleen to those with agenesis of the spleen, the rudimentary spleen of *Doliopoulos & Maillet* might well have been a hypoplastic spleen. The possibility of an accessory liver, nevertheless, seems equally likely.

An almost identical case to that of *Doliopoulos & Maillet* is reported by *Donzelot et al.* (1949). It concerns a 4-year-old female who died on the operating table during operation. The autopsy revealed levocardia, septal defects, pulmonary atresia, patent ductus arteriosus, single ventricle and single A-V valve. In this case, also, there was a transposed rudimentary spleen. It is not reported measured or weighed; nor is it stated to have been examined histologically. The same discussion applies here; the possibility of an accessory liver has not been ruled out.

These two cases are remarkable also because of the age of the patients. Only three cases in the whole material of agenesis of the spleen were 4 years of age or more (4-8 years, *Campbell et al.*, 1953; *Campbell & Forgaes*, 1953). Whether this speaks in favor of agenesis or hypoplasia of the spleen is open to debate.

Summary

Cases with hypoplastic or multiple spleens may show cardiac defects and anomalies of the great vessels indistinguishable from those with agenesis of the spleen.

Four examples of this fact are given in short case reports.

Six random examples from the literature confirm these statements.

The possibility of mistaking an accessory liver for a spleen, grossly, has been pointed out. Two cases in the literature where this reasoning may

apply have been found, and two of the author's own cases with accessory livers without spleens have been referred to.

The significance of hypoplastic or partitioned spleen is difficult to ascertain. The interpretation of the time during embryogenesis when this type of maldevelopment occurred is fallacious.

As the purpose of this study is to catch cardiac deformities that can be assumed to have gone astray at the time of early splenic organogenesis, it would be inviting too many sources of error to include cases with malformed spleens of the type outlined above, especially since congenital heart disease is not a constant feature.

PART IV

Discussion. Cono-Truncus Anomalies and Malformations of the A-V Region, and their Possible Relationship in Cases of Congenital Asplenia

Congenital heart malformations commonly occur as isolated manifestations of dysontogenesis (*Abbott, 1936; Taussig, 1947; Edwards, 1953 a; Rossi, 1954; Kjellberg et al., 1955*). However, syndromes do occur in which malformations of the heart and great vessels are associated with various anomalies in other organs. Syndromes with malformations of the extremities have been described: for example, the Ellis—van Creveld syndrome with ectodermal dysplasia, polydactyly, and chondrodysplasia associated with congenital heart disease, usually an interventricular septal defect (*Ellis & van Creveld, 1940*). Another is Marfan's syndrome, with a tendency to great height, arachnodactyly, looseness of joints, scoliosis, spina bifida, ocular abnormalities, and defects of the cardiac septa, in addition to medionecrosis of the aorta (e.g., *Hsi-Lin Tung & Liebow, 1952*). Moreover, multiple anomalies in association with cardiac defects are found in such a condition as mongolian idiocy (*Taussig, 1947; Rossi, 1954*). The syndromes mentioned, however, contain many variables, and not a constant easily defined single anomaly. *Levinson et al. (1955)* have recently shown, for example, that mongolism is a variable condition without any constant developmental characteristic. Therefore, utilization of the associated defects in the above-mentioned syndromes to time the cardiac defects would be fallacious.

In the present material, consideration has been paid only to cases with heart malformations occurring together with absence of the spleen. That malformations of the cono-truncus and atrio-ventricular region are common without this associated splenic abnormality is obvious. Absence of an organ in childhood is an easily defined congenital abnormality. It has been thought valuable to analyze cases of congenital heart malformations which are associated with an abnormality of another organ, this latter anomaly being a constant feature of all cases. It has to be pointed out, however, that what is implied concerning pathogenesis of the heart malformations in the discussion to follow appears to be relevant only in cases of congenital cardiac defects associated with absence of the spleen.

A. On the Significance of Congenital Asplenia

The common denominator in the material presented is the absence of the spleen. Only autopsy cases with absence of the spleen associated with congenital malformations of the heart and great vessels have been included. A few examples of other splenic anomalies with congenital malformations of the heart and great vessels have been mentioned.

Absence of the spleen is considered rare (*e.g., Kaufmann, 1955*). Its unusually high degree of coexistence with congenital malformations of the heart and great vessels has been repeatedly stressed (*e.g., Putschar, 1934*). This is also revealed in the present material. Eleven of the cases presented have been examined at post-mortem at the Boston Children's Hospital. Twelve cases of absence of the spleen were found by the pathology department of that hospital during the years 1920—1953. The twelfth case, (C.H. A-25—167), as has been mentioned in Part II, Section C (pp. 00) showed purulent meningitis, suppurative otitis, and bronchopneumonia, and no associated malformations of the heart or great vessels. During those 34 years, 7,032 post-mortem examinations were performed on children. From that material the author checked all cases of congenital heart disease for the presence of multiple spleens or asplenia. The occurrence of 11 cases of cardiac malformations among 12 cases of asplenia is in agreement with *Putschar's* finding of 20 with that condition among 23 cases of asplenia in infancy.

To test the hypothesis that congenital heart disease occurs independently of asplenia in the cases presented, a "fourfold" table has been constructed, as shown below.

TABLE 2.

		Spleen		
		absent	present	total
Heart	abnormal	11	341	352
	normal	1	6,679	6,680
	total	12	7,020	7,032

A chi-square test of independence gives a P-value of less than 1:1,000. This shows that the data support the assumption that the occurrence of asplenia and congenital heart disease is correlated.

In adults, however, the association of cardiac malformations and absence of the spleen is found only rarely. *Putschar* mentions 15 cases, including only one with anomalous connections of the great veins and situs inversus of the thoracic viscera (*Bujalsky*, 1829). In adults, as pointed out, for example, by *Boggs & Reed* (1953), it is difficult to ascertain whether absence of the spleen is a congenital malformation or whether the situation is the result of postnatal destruction. The fact that absence of the spleen is associated with malformations of the heart and great vessels more often in children than in adults appears to be due to the severity of the associated anomalies of the heart and vessels. These defects lead to death in infancy or early childhood.

One of the effects that might seem to be due to the absence of the spleen is the occurrence of infections, meningitis in particular. In the material presented four cases had meningitis, not including the above-mentioned case without cardiac anomalies (A-25—167). This might appear to be in accordance with the findings of *King & Shumacker* (1952) who point out the high incidence of meningitis in infants on whom splenectomy was performed before the age of six months. As the cases presented here have severe malformations of the cardiovascular system, it seems, however, dangerous to draw conclusions from this apparent similarity. It is noteworthy, however, that all cases with meningitis in this material died at or before the age of 10 months. This may mean that the function of the spleen in combating infections is more important in early life than later. This has been discussed in Section C of Part II. As presented, the material under consideration does not give any further clues to the explanation of these facts.

However, the *main significance of the asplenia* in this context concerns timing of the associated abnormalities of the heart. As the spleen has been shown to form during the period of critical modeling of the heart, it is assumed that the material collected comprises cases in which the morphogenesis of the heart was disturbed at about the same time during embryogenesis. The absence of the spleen serves as an indication of this period of embryonic development.

The following discussion is based on two assumptions:

1. The absence of the spleen is interpreted as an agenesis, a failure of the splenic primordia to form. It is, in other words, assumed that a spleen was never formed during embryogenesis. Theoretically, it would seem possible that splenic primordia had developed and atrophied later during morphogenesis. An agenesis is, however, still interpreted as being the result of events that went into play at time when the organ in question was about to be formed (*Stockard*, 1921; *Lehmann*, 1955; *Werthemann*, 1955).

2. The early formative stage of development of the spleen is accepted as being its sensitive phase in morphogenesis. This assumption is supported by the views of teratologists, as mentioned. It is only assumed, however, for it has not yet been shown experimentally that the spleen, specifically, can be abolished if it is exposed to teratologic agents during this period. The assumption is supported, however, by the principle that all organs are most sensitive to teratogenic action in their early period of development (*Zwilling, 1955; Wrete, 1955*).

The etiology and pathogenesis of splenic agenesis is unknown. Teratologically it may be due to anoxia, vitamin deficiency, x-ray damage, toxic action of viruses or the influence of placental abnormalities, or it may be genetically determined. Whatever the cause of splenic agenesis may be, it may be assumed to be nonspecific; and however it is induced, the result is dependent on the time of teratogenic action (*Stockard, 1921*).

Various teratogenic agents have different critical periods of action (*Lehmann; Werthemann*), and various organs have their specific critical periods of development (*Zwilling*). The early formative stage of development is still considered to be the critical phase of development (*Zwilling*). This concept includes the exogenous as well as the endogenous (genetic) teratogenic action (*Lehmann; Werthemann*). In the case of exogenous agents, the length of time of exposure seems to play an important role (*Zwilling*). Furthermore, *Stockard* considers that the essential mode of teratogenic action is a decrease in the developmental rate and that the resulting malformation is always due to this slow rate of development.

Thus, the absence of the spleen may be looked upon as a result of developmental arrest ("Hemmungsmmissbildung", *Putschar, 1934*).

B. On Splenic Anomalies other than Agenesis

In Part III a few examples have been given of heart malformations associated with rudimentary or multiple spleens. As these types of splenic malformations may occur without congenital heart disease, as Case 19 shows, the significance of the anomalous spleen is obscure. Nevertheless, some cases have been reported, and examples from the literature have been alluded to, because of the obvious similarity between these cases and those lacking spleens.

As has been shown in Part I on embryology the splenic primordia may have the character of multiple hillocks. *Broman (1921)* describes the first splenic primordia as a poorly outlined area of thickening of the dorsal

mesogastrum that occurs about the end of the first embryonal month. Late in the third embryonal month notching ("Incisuren") appears on the surface that later is smoothed out normally (*Broman, 1921*). In the cases mentioned with multiple spleens it may be assumed that the teratogenic action struck the spleen during the period while these notches existed, causing an arrest of fusion of the incisures. Although the fusion had failed to occur, the spleen continued to grow, and partitioned; or multiple spleens, made up of approximately the normal amount of splenic tissue, resulted.

The period of fusion of the primitive splenic hillocks is not exactly known, nor does the present material give any certain clues to it. It seems likely, for the reasons given, that developmental arrest took place later in these cases of multiple spleens than in those lacking spleens. Although the material is small, this is evident from the heart malformations as well. The teratologic succession of cono-truncus malformations from the primitive and early, to the less primitive and late anomalies under consideration, appears to the author to be the following:

- a) Truncus arteriosus, persistent,
- b) Pulmonary atresia,
- c) Pulmonary stenosis, and
- d) Transposition of the great arteries without stenosis.

In the present material of asplenia, cases of (b) and (c) are most numerous, with 41 cases, or 59 per cent of the whole material (69 cases) belonging to those categories. Cases of (b) and (c) are about equally common, comprising 22 and 19 cases, respectively. Of the seven reported and reviewed cases with multiple spleens, three had pulmonary stenosis (*Lochte, 1898*; *Royer & Wilson, 1908*; *Miller, 1925*), and one had no anomalies of the cono-truncus (*Author, case 16*). None showed atresia of the pulmonary orifice or persistent truncus arteriosus. It should be noted that the case of hypoplasia of the spleen (*Author, case 15*) and cases with "rudimentary spleens" all had atresia of the pulmonary orifice (*Donzelot et al., 1949*; *Doliopoulos et al., 1952*).

However small this material is, it may be inferred that cono-truncus anomalies are less "primitive" in cases with multiple spleens than in those with agenesis of the spleen. To the writer this seems to be evidence that the teratogenous action might have set in later in these cases. In other words, it confirms the method applied, using a malformed organ as an indicator of the approximate time of teratogenic action in "teratologic syndromes".

C. On the Pathogenesis of the Heart Malformations

Description of the *cono-truncus region* was accessible in 67 of the 69 cases, those of *Valleix* (1834) and *Bossert & Leichtentritt* (1920) being excluded. Sixty-five (97 per cent) of these 67 cases were reported to be abnormal, only the cases of *Birch-Hirschfeld* (1871) and *McLean & Craig* (1922) being described as normal in that region.

The *atrio-ventricular region* was adequately described in 58 of the 69 cases excluding the 11 cases of *Martin* (1826), *Valleix* (1834), *Kundrat* (2 cases, 1887 and 1888), *Garvin* (1927), *Bossert & Leichtentritt* (1920), *Jaccard* (1951), *Gasser & Willi* (case 2, 1952), *Boggs & Reed* (2 cases, 1953), and *Bush & Ainger* (1955). The cases of *Jaccard* and *Gasser & Willi* (case 2) were examples of *cor biloculare* and can be assumed to have contained common atrio-ventricular ostia although no descriptions of the atrio-ventricular valves have been included in the reports. The cases of *Boggs & Reed* were examples of hearts with large interatrial and interventricular septal defects (question of *cor biloculare*); no adequate description of the atrio-ventricular valves is included in the report. In Case 1 there was pulmonary atresia. Despite this fact, the authors state, "except for the right-sided position of the aortic valve, the remaining valves were not unusual". In their Case 2 they state, "the aortic, mitral and tricuspid valves were not remarkable except in position". In *Bush & Ainger's* case the tricuspid valve is described and stated to be situated to the left, while the right-sided atrio-ventricular valve is not described at all. Of the mentioned 58 cases with adequate descriptions of the atrio-ventricular valves, 56 (97 per cent) showed abnormal atrio-ventricular ostia, as accounted for in Section C of Part II (pp. 00), the two cases of *Birch-Hirschfeld* and *McLean & Craig* being described as normal. If the cases of *Jaccard*; *Gasser & Willi* (case 2); *Boggs & Reed* (2 cases); and *Bush & Ainger* are included, the percentage would be the same (61 of 63 cases).

All cases with abnormal atrio-ventricular regions had malformations of the *cono-truncus*. All cases with malformations of the *cono-truncus* and adequate descriptions of the atrio-ventricular region showed the latter to be anomalous. Two cases, (*Birch-Hirschfeld*, 1871; *McLean & Craig*, 1922), with adequate descriptions of both regions showed them to have normal *cono-truncus* and *A—V* regions.

1. Isolated occurrence of *cono-truncus* and *A—V* anomalies

The pathogenesis of *cono-truncus anomalies* has been studied extensively since the time when *Rokitansky* (1875) proposed a theory explaining transpo-

sition of the great arteries, stenosis of the arterial ostia and septal defects on the basis of a primary deviation of the septation process. This theory, later extended by *Geipel* (1899 and 1903) and *Mönckeberg* (1924), was opposed by *Spitzer* (e.g., 1923; *Spitzer, Lev & Vass*, 1951) who claimed to be able to explain all malformations of the heart on the basis of his phylogenetic theory. *Spitzer*, regarding transposition, emphasized detorsion of the conus as the cause of obliteration of the normal (left) human aorta that was replaced by a persistent reptilian (right) aorta evanescent in the human embryo. This concept was strongly opposed by *Pernkopf & Wirtinger* (1933 and 1935) who, on the basis of ontogeny, regarded inversion of the conus with growth of an abnormal septum as the essential cause of transposition. Excellent discussions of the above theories will be found in papers by, for example, *Harris & Farber* (1939), *Bredt* (1935/36 and 1936) and *Doerr* (1938, 1943, and 1955 a).

Isolated malformations of the *atrio-ventricular region* are more rare than those of the *cono-truncus*. Anomalies of the A—V region are not as easily detected at post-mortem examination as are *cono-truncus* anomalies. The latter are usually obvious as soon as the pericardial cavity is opened. The anatomic variation in malformations of the *cono-truncus* is greater than in those of the *atrio-ventricular region*. For these reasons, the literature on malformations of the *atrio-ventricular region* is comparatively scarce. Among classical studies, those of *Sato* (1914) and *Mönckeberg* (1915 and 1924) may be mentioned.

Recently there has been great interest in the surgical correction of interatrial septal defects and anomalous venous connections (*Gross*, 1953; *Kirklin*, 1953; *Geraci & Kirklin*, 1953). The clinical diagnosis of interatrial septal defects and anomalous venous connection is becoming more accurate by the addition of new techniques (e.g., *Varnauskas & Werkö*, 1954; *Kjellberg, Mannheimer, Rudhe & Jonsson*, 1955). Possibly for these reasons, there is an increasing interest in anomalies of the "venous end of the heart". This is reflected by a gradually expanding literature on this subject. Among American pathologists who have published several papers on the malformations of this region of the heart is *Edwards* (*Rogers & Edwards*, 1948; *Edwards & Burchell*, 1949; *Edwards & DuShane*, 1950; *Edwards*, 1953 b; *Becu, Tauxe, DuShane & Edwards*, 1955). Also, German pathologists have recently made important contributions to the pathology of this region (*Doerr*, 1952 a and b; *Kiss, Partilla & Pernkopf*, 1954). *Doerr* (1955 a), mentions that his coworker, *Kl. Goerttler*, is occupied with a study on the transposition of the veins. Embryologists also have recently contributed important studies on this region, as evidenced by *Shaner's* papers (1949 and 1951).

2. Malformations of the cono-truncus and the A—V region in asplenia as a pathologic complex

The isolated occurrence of cono-truncus anomalies and malformations of the atrio-ventricular region has thus been thoroughly investigated, as is evident from the references quoted above. However, anomalies of one of these regions, associated with malformations of the other, have aroused comparatively little interest. The studies performed have been limited largely to cases of mitral or tricuspid atresia. These malformations of the atrio-ventricular region are always, in tricuspid atresia, and often, in mitral atresia, associated with anomalous cono-truncus regions (*Edwards, 1953 a*). Mitral atresia is often combined with aortic atresia. Tricuspid atresia is always associated with some anomaly of the cono-truncus, as, for example, pulmonary stenosis (atresia) or transposition of the great arteries.

The possible *linkage* of malformations of the two regions has been mentioned in tricuspid atresia (*Bredt, 1935/36; Lev, 1953 b*). *Spitzer (1951)* pictured an influence of the cono-truncus anomalies upon the atrio-ventricular region, causing for example, transposition of the A—V ostia.

Shaner's (1949 and 1951) valuable embryologic approach led to the theory that anomalous atrio-ventricular canal cushions might cause malformations of the cono-truncus region of the heart. While dissecting 15,000 pig embryos, *Shaner (1949)* encountered 35 with abnormal hearts. Fifty per cent of these showed anomalous A—V canal cushions. *Shaner* considers that the anomalous A—V canal cushions of these hearts prevented the normal migration of the aorta into the left ventricle. He considers this migration essential to the normal evolution and septation of the cono-truncus, and arrest of it would result in malformations of that structure.

This concept corresponds well with the hypothesis of *Doerr (1938)* that the shape of the entire cono-truncus is decisive in its normal or abnormal septation. Supported by *Shaner's* observations on pig embryo hearts, *Doerr (1952 a and b; and 1955 a)* further elaborates this concept. *Doerr (1952 b)* considers the incidence of A—V anomalies associated with congenital pulmonary and aortic stenosis, 30 and 50 per cent, respectively, as evidence that A—V anomalies are primary to those of the cono-truncus in *certain* cases of heart malformations, mentioning congenital stenosis of the aortic and pulmonary ostia as examples.

As pointed out by *Bredt (1935/36 and 1936)* a *linkage* between anomalies of different portions of the heart ("gekoppelte Missbildungen") may, theoretically, be divided into two main groups,

- I. Dependent (conditional) linkage,
 - a) equivalent and mutually independent (due to the same cause),
 - b) reciprocally dependent (cause-effect relationship),
- II. Absolute (unconditional) linkage,
 - a) equivalent and mutually independent (due to the same cause),
 - b) reciprocally dependent (cause-effect relationship).

Group I concerns an association of anomalies that is not constant, but may occur under given circumstances. Group II comprises anomalies that are always associated, so that if a certain anomaly occurs the other must be present.

In an extensive discussion on the subject of linkage, *Bredt* (1935/36) considers that most of the linked anomalies, as, for instance, tricuspid atresia, are examples of Group I (a). It should be pointed out that his discussion is concerned only with linkage between *anomalies per se*. If, however, a *linkage between malformed regions* is accepted instead of between specific malformations, such a condition as tricuspid atresia would be an example of Group II. This reasoning is valid, as tricuspid atresia is always associated with malformations of the cono-truncus, as mentioned previously. The associated malformations of the cono-truncus are either stenosis (atresia) or transposition. Whether the associated anomalies in tricuspid atresia are linked in an (a) or a (b) fashion is not clear. It remains to be evaluated whether tricuspid atresia and the associated cono-truncus anomaly are due to the same cause, or whether there is a cause-effect relationship.

The discussion on the pathogenesis of tricuspid atresia (*Bredt*, 1935/36; *Edwards*, 1953 a) is impaired by lack of evidence of the time during morphogenesis when development of the heart was disturbed. Assisted by facts like the presence of valvular tissue in an atretic pulmonary orifice, or the presence of an interventricular septal defect, timing of the tricuspid atresia has been attempted (see *Edwards*, 1953 a). The time during embryogenesis when the atresia of the tricuspid orifice occurred is likewise unknown. There is no unanimity of opinion about whether atresia occurred before or after partitioning of the atrio-ventricular canal (*Bredt*, 1935/36; *Edwards*, 1953 a).

Equally obscure is the coexistence of mitral and aortic atresia that may occur (*Edwards*, 1953 a). This coexistence would be an example of Group I in the above outline, as mitral and aortic atresia may occur separately. *Edwards* (p. 406 b, 1953 a) points out that "for some occult reason there seems to be a secondary fusion of the developing [aortic] cusps". In these cases, *Edwards* seems inclined to accept fetal inflammation (*Farber & Hubbard*, 1933) as the most likely cause of the atretic aortic orifice.

In this context it may be interesting to note that the present material contains five cases of mitral atresia but not a single instance of aortic atresia. Examples of pulmonary atresia are, however, numerous (22 cases). The absence of aortic atresia cases would perhaps indirectly tend to support the hypothesis of *Farber & Hubbard* (1933) of this malformation's being the result of fetal inflammation, if, in the present material, developmental arrest not due to fetal inflammation should be accepted as the cause of the cardiac malformations present.

As pointed out above, the usual difficulty in understanding the developmental basis for any given malformed heart is the lack of knowledge of the time when the development of the heart went astray. In the present material there is a common denominator outside the heart that may be taken as an indicator of that time, the absence of the spleen.

It was shown by the author in Part I that early splenic primordia exist while the cono-truncus and the atrio-ventricular region are being partitioned. There is evidence that the fusion of the atrio-ventricular canal cushions occurs before the septation of the cono-truncus is completed. The final differentiation of the A-V canal cushions into valves, however, is accomplished after the complete separation of the cono-truncus.

The early formation of the spleen is accepted, teratologically, as its most sensitive stage of development (Assumption 2). The malformed hearts in the present material show anomalies of structures that appear to be in a critical phase of modeling during early splenic organogenesis. It follows that the teratogenic action on the heart and spleen took place simultaneously.

Agenesis of the spleen is accepted as the result of developmental arrest ("Hemmungsmisbildung", *Putschar*, 1934). It seems logical to look upon the malformations of the heart and great vessels presented here as examples of arrested development. Most authors agree that congenital malformations of the heart are usually due to developmental arrest (*e.g.*, *Bredt*, 1936; *Dörr*, 1955 a).

That organogenesis has been interrupted in the cases under consideration is further supported by the following evidence. The septation of the heart has been interrupted, as shown by the presence of 32 cases of cor biloculare. Further proof of septation arrest is furnished by the occurrence of 18 cases with defects in the area of the ostium primum, the cor biloculare cases not included. Interruption during embryogenesis of the normal resorption of the common pulmonary vein (*Buell*, 1922; *Auer*, 1948) occurred in 20 cases. In 36 cases the development of the pulmonary venous channels stopped at various levels, thus establishing connections with various systemic channels, including the right atrium, and resulting in anomalous pulmonary venous

connections. Systemic veins also display interrupted development, showing anomalous connections in 31 cases, including only those in close proximity to the heart.

Thus it has been shown that:

1. The heart malformations under consideration may be looked upon as being the result of developmental arrest;
2. the absence of the spleen in these cases is looked upon as the result of arrested development occurring in early splenic formation;
3. as the spleen is absent in all cases, it may be assumed that the organogenesis of the heart in all cases was disturbed at approximately the same time;
4. the malformed hearts display a high proportion of atrio-ventricular anomalies of various types (97 per cent);
5. there is also a high incidence of cono-truncus anomalies (97 per cent);
6. all cases showing atrio-ventricular anomalies have malformations of the cono-truncus;
7. all cases with malformations of the cono-truncus and adequate description of the atrio-ventricular region have malformations of the latter; and finally,
8. that the two cases with *normal* cono-truncus regions also had *normal* atrio-ventricular regions.

So far, the following *general conclusion* is achieved: in cases of congenital heart malformations displaying absence of the spleen, there appears to be a linkage between the atrio-ventricular and cono-truncus regions of the heart, malformations of one region always being associated with malformations of the other. This general conclusion is valid only under the condition stated, that is, only when the spleen is absent.

In order to investigate a possible presence of a linkage between the cono-truncus and the atrio-ventricular region in asplenia, a chi-square test on the independence of these two regions has been carried out, giving a P-value of less than 1: 1,000. The data therefore support the assumption of the linkage mentioned.

If there is an absolute linkage between the two regions of the heart in cases of agenesis of the spleen, two theoretically different mechanism may have been in operation to produce the anomalous regions. In the theoretical classification of linkage, there are two subgroups of each of the two main groups. The question of whether there may be a cause-effect relationship between the malformations of the cono-truncus and atrio-ventricular region, or whether the malformations of the two regions are due to the same cause must be discussed.

3. Question of whether malformations of the cono-truncus and A—V region in asplenia are due to the same cause

A simultaneous and independent teratogenic action on the two regions of the heart must be considered, particularly as the anatomic variation of the anomalies is so wide. There is no constant occurrence of one type of cono-truncus malformation always being associated with one type of atrio-ventricular anomaly. In the present material the cono-truncus displays three types of malformations: persistent truncus arteriosus, pulmonary stenosis (atresia), and transposition of the great arteries. The atrio-ventricular region also exhibits a variety of malformations. In the material presented, the variation in the pathology of that region is even greater than in that of the cono-truncus. There are a common A—V ostium with varying numbers of cusps, mitral atresia, tricuspid atresia, and double bicuspid A—V valves. As far as the specific malformations are concerned, there is no constant linkage.

Apart from the wide anatomic variations of anomalies in these regions, there is another reason to consider an independent teratogenic action on the cono-truncus and atrio-ventricular region. They have one tissue component in common, the gelatinous reticulum. This substance is vital for the division of the A—V canal and the septation of the cono-truncus. Hypothetically, an arrest of the growth rate of this substance would seriously interfere with the normal evolution of these structures.

There are different mechanisms that might produce inhibition of growth in general, and probably of the growth of the gelatinous reticulum as well. *Oxygen deficiency* may cause cardiovascular anomalies as has been shown experimentally (e.g., Schellong, 1955). After prolonged oxygen deficiency the concentration of ribonucleic acid is lowered in embryonal tissue, as shown experimentally (Leder, 1955). Ribonucleic acid decreases gradually during embryonic life as protein synthesis is diminishing (Caspersson & Thorell, 1941). It follows, theoretically, that hypoxia of the gelatinous reticulum would lower the growth rate of the substance and thus interfere with septation.

There is a high incidence of cono-truncus anomalies in the offspring of pregnant rats after being fed a diet deficient in pteroylglutamic acid (Baird et al., 1954). *Antifolic acid* is known to be a growth inhibitor and it may have acted on the gelatinous reticulum, causing abnormal septation. In their paper, Baird et al. preliminarily reported the cono-truncus anomalies, and stated that histologic studies of the early phases of cardiac development were in progress. These authors did not report any associated defects of the

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atrio-ventricular region. Possible defects in the latter region would not be clearly revealed on gross examination of newborn rats.

Another mechanism resulting in mutually independent defects of the cono-truncus and atrio-ventricular region is proposed by *Farber & Hubbard* (1933). They suggested that *fetal endomyocarditis* might be accepted as a causative factor in producing stenosis (atresia) of the cardiac ostia without the resulting anomalies necessarily being linked in a cause-effect sense. In the present material, however, the evidence points in the direction of developmental arrest, as shown by the association of numerous malformations of other organs. In the cases concerned there is no evidence of end results of inflammatory processes in the conventional sense. However, theoretically, inflammation may be accepted in general as a possible cause of developmental arrest, although this reasoning does not seem to apply here.

Thus, there is experimental evidence that may point in the direction of malformations of the cono-truncus and the atrio-ventricular canal being due to the same cause, a possible defect in the gelatinous reticulum.

In the experimental work on animals so far published, no report has been given on the association of cardiac anomalies and absence of the spleen. This may not be relevant in one way or another, as the consequences of such an association depends on the formation of the spleen and cardiogenesis being synchronous. This synchronism has been shown by the writer to exist in man. The animal still has to be found in which the spleen is formed during the same phase of cardiogenesis. To gain experimental support for the association of atrio-ventricular anomalies with splenic agenesis it is important to know at what period in cardiogenesis the spleen appears in the animal in question. On this point, therefore, further investigations are necessary.

In summary, an unknown teratogenic agent might have acted on the cono-truncus and atrio-ventricular region independently. Thus, this mechanism cannot be ruled out as an explanation of the pathogenesis of the associated cardiac malformations.

4. Question of whether there is a reciprocal dependence between the cono-truncus and the A—V region in cases of asplenia with congenital cardiac malformations

Even if it cannot be ruled out that the abnormal atrio-ventricular and cono-truncus regions are the result of the same teratogenic action and that they are independent of each other, there are facts in the present material that tend to contradict this view. First, there is a high incidence of cono-truncus anomalies, 97 per cent. Second, atrio-ventricular malformations occur

in 97 per cent of the cases (a slightly smaller group, due to inadequate description of this region). Third, the atrio-ventricular anomalies are always associated with malformations of the cono-truncus in this material. Fourth, all cases with anomalies of the cono-truncus have malformations of the atrio-ventricular region, if only cases with adequate description are considered. Although the material is small, comprising only 69 cases, these circumstances are very unusual.

Doerr (1952 b) found in cases of congenital pulmonary and aortic stenosis that the atrio-ventricular region was anomalous in 30 per cent of the first and 50 per cent of the second. In transposition of the great arteries, *Doerr* found abnormal A—V regions in 33 per cent. In malformed pig embryo hearts, *Shaner* (1949) encountered anomalous atrio-ventricular canal cushions in 50 per cent of cases with cono-truncus malformations. These figures may appear low in comparison with the incidence in the present material. The reason for this apparent discrepancy seems to lie in the method of selection of the material presented here. The high incidence of A—V anomalies in this material seems to be indirect evidence that this region was disturbed synchronously with the spleen.

The question of whether one region may be primary in causing defects of the other in cases of asplenia seems difficult to answer. There is coexistence of malformations of the two regions in all cases, and if one region is normal, the other is also normal. However, in the light of recent observations, a discussion of some of the possible mechanisms in producing the linkage described in the material presented may not be entirely barren.

In the section on embryology (Part I) reference has already been made to *Doerr*'s concept of the conflict zone between the cono-truncus and the atrio-ventricular canal. The atrio-ventricular aspect of this Achilles heel of the developing heart is considered by *Doerr* to be the essential target of teratogenic action in certain heart malformations. Obviously, this is in harmony with the findings of *Shaner*. According to *Shaner* and *Doerr*, malformations of the cono-truncus in certain cases will be understood if consideration is paid to malformations of the atrio-ventricular canal cushions. *Doerr* points out that the level of the future aortic and pulmonary valves is the same as that of the atrio-ventricular canal immediately before division of the latter and septation of the former. *Shaner* and *Doerr* picture the possibility of malformed canal cushions being an obstacle for the proper torsion (*Doerr*) of the cono-truncus and its migration (*Shaner*) into the left ventricle.

The vectorial torsion of the conus in the sense of *Doerr* seems to be a prerequisite for normal septation, a fact that is supported by the perfusion

experiments on glass models of embryonic hearts performed, for example, by Bremer (1931) and Kl. Goerttler (1955). Thus, septation of the cono-truncus may be looked upon as the result of the spiraling currents of blood rather than as a cause of the blood circulation. This is well shown by Bremer (1931) in the living chick embryo heart before septation has occurred, and by Kl. Goerttler (1955) on glass models of human embryonic hearts before septation.

As the spiraling currents have been shown to appear before septation is achieved they may be assumed to play an important causative role in partitioning. If the proper migration and torsion of the cono-truncus is interfered with, normal spiraling would be upset and would then cause abnormal septation because the zones of lessened lateral pressure ("seitendruckfreie Zonen" of Kl. Goerttler) would change.

One possible mechanism that would interfere with the proper migration and torsion of the cono-truncus is developmental arrest of the atrio-ventricular partitioning. Teleologically, the atrio-ventricular region would not be able to receive the migrating truncus between its right and left components if the fusion of the canal cushions did not occur at the proper time. As septation of the cono-truncus is well under way at the time of fusion of the canal cushions, it might proceed, but presumably in an abnormal fashion, causing various anomalies of the cono-truncus.

Four examples from the literature may be said to illustrate this possible arrest of migration resulting in cono-truncus anomalies. Bredt (1935/36) describes two cases in which the auricular appendages were found to the left of the arterial trunks. He refers to two further cases from the literature (Dünner, 1914; Kettler, 1932). In these four cases the arterial trunks were situated unusually far to the right. There was tricuspid atresia or stenosis in all cases.¹

In the present material there is a variety of atrio-ventricular anomalies. The most frequent of these is a common atrio-ventricular ostium. This occurred in 46 of 58 cases with adequate descriptions (79 per cent). In these instances, in other words, normal fusion of the A-V canal cushions had not occurred. It is conceivable that this failure of fusion might have been able to arrest the proper migration and vectorial torsion of the cono-truncus in the sense of Shaner and Doerr. These events are considered to be prerequisites for the blood currents to spiral around each other in such a way as to cause normal septation (the slack-water theory of Bremer, 1931; Patten, Kramer & Barry, 1948). If the slack-water theory for the septation of the cono-truncus is accepted, it seems conceivable that, theoretically, an undivided atrio-ventricular canal might upset the shape and localization of the cono-

¹ See addendum on p. 110.

truncus so as to cause abnormal spiraling of the blood currents and abnormal septation of the cono-truncus. If, for example, the truncus arteriosus is straightened out, during its migration, by influence from the abnormal atrio-ventricular cushions the prerequisite for spiraling would be abolished; and the circumstances required for a persistent truncus arteriosus would result.

This admittedly grossly mechanical approach is not so easy to apply to the remaining atrio-ventricular anomalies present. In cases of *mitral* or *tricuspid atresia*, for example, it seems difficult to lay the responsibility for the associated cono-truncus malformations on the atrio-ventricular anomaly. *Lev* (1953 b) is, however, inclined to explain the pathogenesis of the various complexes associated with tricuspid atresia as being directly due to the latter anomaly. *Lev* seems to arrive at this conclusion mostly on hemodynamic grounds. From the morphologic point of view, a delayed fusion of the A-V canal cushions has to be considered as a possibility. From Part I it may be recalled that the division of the A-V canal is very close in time to the complete division of the cono-truncus. Morphologically, it is possible that a delayed fusion of the A-V canal cushions did occur, interfering with cono-truncus migration. Later, then, there was abnormal division resulting in atresia of one A-V ostium. Functionally, it must be recalled that the blood streams always have to pass the atrio-ventricular canal before they reach the cono-truncus. Thus, any modification of the blood streams occurring at the A-V ostium might be perpetuated in the cono-truncus. Considerations of the functional aspects of these events must be entirely speculative, but will be briefly considered in a later section.

If a cause-effect relationship between the malformations of the cono-truncus and the atrio-ventricular canal is accepted, the question arises as to whether the cono-truncus anomalies might be primary to those of the A-V region. *Spitzer* (1951), for example considered anomalous A-V ostia associated with cono-truncus malformations to be secondary to the latter. He specifically mentions transposition of the A-V ostia in this respect. *Spitzer* appears to accept this as the mechanism whenever malformations of the two regions are associated. Differentiation of the heart proceeds in a cephalo-caudad direction, that is from the cono-truncus to the sino-atrial end (*Patten*, 1949; *Copenhaver*, 1955). In accordance with the teratologic views quoted earlier, the early formative stage being considered more sensitive, the cono-truncus would be in its critical stage of development earlier than the atrio-ventricular canal. Although it is true in general that morphologic differentiation proceeds in a cephalo-caudad direction, there appears to be division of the atrio-ventricular canal by fusion of its cushions before septation of the cono-truncus is completed. In the phase of division of the A-V canal it might be

more sensitive towards teratologic action than the cono-truncus. In addition, there are normally two blood streams separated by gelatinous reticulum in the area of the atrio-ventricular canal before this happens in the cono-truncus region. Moreover, the two blood streams might be changed by an abnormal A-V region so as to upset the normal blood currents of the cono-truncus. This will be briefly discussed in a later section.

Early splenic formation has been shown to occur during fusion of the A-V canal cushions and before the septation of the cono-truncus is completed. The spleen is absent in all 69 cases presented here. There is a large number, 46 cases, in which fusion had failed to occur. In 12 other instances there were other A-V anomalies. In 97 per cent of the cases with adequate description of the A-V region there were A-V anomalies. To the writer this is evidence in favor of the view that these anomalies might have been primary to those of the cono-truncus in cases of agenesis of the spleen.

5. A short comment on the phylogeny of heart and spleen

The present material shows interesting analogies from the phylogenetic point of view. Thus, the spleen is absent in the lung-fish (*Dipnoë*) according to anatomists (e.g., Müller, 1916). The lung-fish shows phylogenetically the first evidence of a primitive interatrial septum, although it is functionally still a *cor biloculare*. In the next step in phylogeny, in the amphibia, the interatrial septum is "complete", and the spleen appears for the first time in phylogeny as a separate organ. These factors would invite speculations in the direction of Spitzer's phylogenetic theory of heart malformations. In the opinion of the writer, however, these facts only emphasize the pitfalls in analogies. It is always easy to find similarities between simple objects; and the reported malformations of the heart and great vessels tend to be simple rather than complex from the embryologic point of view.

6. On the possible relationship between morphology and physiology of the developing heart

In the preceding sections attention has been paid to morphology and the interrelationship of topographic structures in trying to explain the possible events that may lead to malformations of the cono-truncus in linkage with the atrio-ventricular region. Functional considerations, however, may add some important view-points to the understanding of the conditions under which the embryonic heart develops, and may cast some light on possible mechanisms that might have produced the malformed hearts described.

The first heartbeat in chick embryos occurs at about the 9-10 somite stage

(Sabin, 1920; Patten, 1933 and 1949), at which time the embryo chick heart is practically all ventricle and almost a straight tube. The contraction observed occurs in the right aspect of the common ventricle and proceeds in a caudo-cephalad direction. This is confirmed by electrocardiographic studies by Hoff *et al.* (1939).

During this period of development and up to the time of the formation of proper atrio-ventricular and semilunar valves the valvular function of the heart is handled by the cardiac jelly of Davis (1924 and 1927), by its being heaped up into mounds (Patten, Kramer & Barry, 1948). These authors have shown that the valvular pads consisting of cardiac jelly mounds are formed at the level of the future semilunar valves and at the site of the future atrio-ventricular valves. These mounds act in a reciprocal fashion, the closure at the atrio-ventricular level occurring "just after the sweep of contraction through the atrium has fully charged the ventricle with blood, and remaining closed while blood is being forced out through the conus". The contraction wave reaches the conal pads at the end of ventricular systole, thereby checking regurgitation. At this time the atrio-ventricular pads of cardiac jelly are open to permit filling of the ventricle for the next cycle.

Patten (1949) points out three important factors in the efficient propulsion of blood by the tubular heart:

1. The shifting of the pacemaker's location at different ages of the embryo, with its being constantly situated at the intake end of the heart, this being the start of propulsion.
2. The development of the above-mentioned valvular pads of cardiac jelly before the morphologic differentiation of valves proper, these minimizing the regurgitation and adding efficiency to the propelling force, and
3. adequate stroke volume (Barry, 1948).

This third factor, that might be called Barry's law of the embryonic heart, as equivalent to Starling's law of the adult heart, is actually the functional evaluation of the morphologic cardiac jelly of Davis. Barry points out that the systolic diameter of the tubular heart must be practically zero to keep up a cardiac output sufficient for the needs of the embryo. Further, the filling of the ventricle as well as its output depends on the diastolic diameter of the myocardial sleeve. Neither adult nor embryonic myocardium can shorten, in systole, more than a definite proportion of the diastolic length. If the stroke volume is going to be maintained, it follows that the embryonic myocardial diameter must be considerable. The thick layer of cardiac jelly, at least 45 per cent of the radius of the lumen in diastole, will transmit the

force of contraction radially against the small lumen. The circumference of the contracted myocardium is relatively large while the lumen is practically closed as its radius is increased by the thick layer of cardiac jelly. Thus, the cardiac jelly will increase the diastolic diameter of the myocardium enough for an adequate stroke volume.

Considering these facts in pondering the pathogenesis of the heart malformations in the present material, it would seem possible that any change of the cardiac jelly (gelatinous reticulum) at the region of future valves would seriously interfere with the physiology of the heart in the embryo. If the cardiac jelly should degenerate at the atrio-ventricular valves, this would result in regurgitation during systole, a process that would probably not improve the morphogenesis of the heart. In the cases with a common atrio-ventricular ostium, fusion of the canal cushions had failed. Presumably, this means that damage to the cardiac jelly had occurred here.

Any process that interferes with the proper function of the cardiac jelly would probably interfere with embryonal heart function. An arrested division or an abnormal fusion resulting in a common A-V ostium or an atretic A-V ostium may alter the physiology of the heart in the embryo in such a way as to cause malformations of other regions. The malformations would be linked in a physiologic sense.

These speculations by the author are based on experimental work on normal chick embryos (*Bremer, 1931; Patten, Kramer & Barry, 1948*). Mapping out the physiology of the abnormal embryo heart seems necessary to evaluate the role of altered hemodynamics as a cause of congenital cardiac malformations.

7. Practical and clinical considerations

It has been shown that in cases of congenital asplenia associated with congenital malformations of the heart and great vessels there is a high incidence of cono-truncus and A-V anomalies. The view of the writer is, that, in asplenia, the A-V anomalies may be primary to those of the cono-truncus. Whether or not this is accepted, it seems important to stress the frequent occurrence of the latter. The present study has been confined to cases lacking spleens, and it is possible that the close correlation between anomalous cono-truncus and A-V regions exists only in those cases. However, for the understanding of cono-truncus anomalies in general it seems important, in view of the evidence presented, that the A-V regions of all such cases should be studied with meticulous care at autopsy.

Furthermore, the material presented contains a large number of cases

with anomalous venous connections. It should be stressed that the mapping of these is possible only when dissection *in situ* is carried out. After the vessels have been severed, it is often impossible to trace their course and their connections. In the new cases presented here this *in situ* dissection has been the procedure.

A few clinical features of the cases of asplenia will be mentioned. This syndrome occurs most commonly in males. Of the 63 cases of this report in which the sex was stated, 40 were males and 23, females. Various races are represented: among them are two Negroes (*Shapiro*, 1930; *Leikin*, 1951); one is Chinese (*Hu*, 1929); and one is Japanese (*Kimura*, 1930). In 65 cases the age at the time of death was stated. Most of the cases, 55, fall within the age range of birth to 12 months. The stillbirths have not been included.

In four cases in which the clinical diagnosis of Tetralogy of Fallot was made operations were planned or performed (*Boggs & Reed*, case 2, 1953; *Polhemus & Schafer*, cases 2 and 3, 1952; *Campbell et al.*, case 3, 1953). Shunt operations in these cases were either followed by death shortly afterwards, or they failed because of hypoplasia of the pulmonary arteries or atresia of the pulmonary trunk, making an anastomosis impossible. It would seem necessary to rule out the Type B syndrome of asplenia in clinical cases of Tetralogy of Fallot before operations in the latter condition are considered. That cases with rudimentary spleens also may mimic an uncomplicated Tetralogy of Fallot, is shown by the two cases of *Donzelot et al.* (1949) and *Doliopoulos et al.* (1952). As mentioned in Part III, these cases masqueraded clinically as examples of Tetralogy of Fallot. Operations resulted in death shortly afterwards. Roentgenologic examination of the abdomen to establish the position of the stomach, the shape of the liver, and a possible asplenia seems advisable in cases of suspected Tetralogy of Fallot to rule out the syndrome under consideration. Minor surgical procedures have been followed by death in three cases. In *Bossert & Leichtentritt's* (1920) case death followed an adenoidectomy, the cause of death being meningitis. In *Kimura's* (1930) case incision of an atretic anus resulted in death shortly afterwards. In Case 6 of *Campbell et al.* (1953) death followed a tonsillectomy that was performed before a planned shunt operation.

A persistently increased number of Heinz bodies in the peripheral blood has been stressed by *Gasser & Willi* (1952 and 1955) to aid in the diagnosis of this syndrome. They also found Howell-Jolly bodies in their cases (1955). It should be pointed out, however, that Heinz bodies by no means occur only in cases of asplenia, but may be found, for example, after administration of various benzene compounds, and in certain hemolytic anemias (*Hartmeier*, 1953; *Dacie*, 1951). Heinz bodies have also been produced experimentally

after administration of methylene blue (*Spicer & Thomson, 1949*). In none of the new cases presented, were Heinz bodies looked for clinically. They are destroyed by most fixatives (*Dacie*).

In relation to etiology of asplenia, the teratologic syndrome of visceral symmetry, it may be mentioned that there was no known instance of any of the mothers' being exposed to rubella, nor was there any family relationship among the 14 new cases presented. There is in the literature a very slight suggestion that there may be a familial occurrence. *Polhemus & Schaffer's (1952)* Case 3 is reported to have had a sibling with multiple spleens and congenital heart disease with a common atrio-ventricular ostium at autopsy. *Gasser & Willi (1952)* consider it quite certain that the causative factor is endogenous, a lethal factor with pleiotropic effects. The present material does not give any clues to the etiology.

Summary and Conclusions

Part I. Six embryos measuring 9—12 mms. in greatest length have been shown by the writer to contain early splenic primordia in the left aspect of the dorsal mesogastrum. The embryos belong to Horizons XV—XVII of Streeter, thus their ovulation age is estimated to be 31—36 days. Temporal relations of splenic formation to cono-truncus septation and division of the A—V canal have been discussed. This last is divided before septation of the cono-truncus is completed (Streeter). The author has shown that early splenic primordia exist at the time of fusion of the A—V canal cushions, in Horizon XVI. At the same time there is initiation of pulmonary lobation, and there is a primitive gut mesentery.

Part II. Congenital absence of the spleen (asplenia) is rare. At the Boston Children's Hospital it was found 12 times in an autopsy series comprising 7,032 post-mortem examinations. Eleven of them were associated with congenital malformations of the heart and great vessels. Asplenia associated with malformations may be said to constitute a syndrome. It is suggested by the writer that it be called "asplenia, a teratologic syndrome of visceral symmetry".

Data on autopsy cases of asplenia associated with congenital cardiovascular anomalies have been compiled in this study. Such a selection has been made in order to pick up cases of hearts whose formation may be assumed to have gone astray at approximately the same time, that is, when the spleen should have been formed during embryonic life.

Fourteen new cases of this syndrome are reported, and 55 cases have been collected from the literature. Cono-truncus anomalies occur in 65 of 67 cases of asplenia (97 per cent). There are three types. Type A, persistent truncus arteriosus, contains 10 cases; Type B, pulmonary stenosis or atresia, comprises 41 cases (19 with stenosis and 22 with atresia); Type C, transposition of the great arteries without pulmonary stenosis or atresia, 14 cases. There are two cases, Type D, with normal cono-truncus regions, and two cases without available descriptions of this region. In Type A, four of the cases are the writer's; in Type B, seven (four with stenosis and three with atresia); and in Type C, three cases.

The atrio-ventricular region is abnormal in 56 of 58 cases with adequate

description (97 per cent). These anomalies vary in type; a common A—V ostium is present in 46 cases, or in 79 per cent. Moreover, there are cases of tricuspid atresia or mitral atresia. The two cases with normal cono-truncus had normal A—V regions.

The cardiovascular anomalies are looked upon as due to developmental arrest. Thus, there are 32 cases of *cor biloculare*, and 18 additional cases have defects in the area of the *ostium primum*. In 36 cases there are anomalous pulmonary venous connections, total or partial. In 19 cases there are bilateral superior vena cavae. A new classification of this anomaly is proposed. In 46 instances there is abnormal lobation of the lungs; in 40 of these the lobation is symmetric; and in 35, each lung had three lobes. The liver is transposed in 17 cases and symmetric in 31 cases. The stomach is transposed in 33 instances. There is a common mesentery in 33 cases.

Serious infections occurred in a number of cases. They were more common under the age of 10 months. Five instances of meningitis are present in 66 cases of asplenia, including one case without cardiovascular anomalies. These facts are discussed briefly in relation to the occurrence of infections reported after splenectomy in infancy. The incidence of meningitis in congenital heart disease associated with asplenia does not appear to be significantly higher than in such cases with spleens.

Part III. Multiple spleens or rudimentary spleens may occur together with cardiovascular anomalies similar to those encountered in cases of asplenia. Four new cases of this association are reported, and six examples from the literature are mentioned. One additional case of multiple spleens without cardio-vascular anomalies is reported. The significance of multiple spleens and the possibility that this defect occurred later in embryogenesis than asplenia are discussed. The associated cardio-vascular anomalies furnish some support for this possibility. Accessory livers were found by the author in two cases of asplenia. The possibility of confusing an accessory liver with a rudimentary spleen is stressed and discussed.

Part IV. The pathogenesis of the cono-truncus anomalies in cases of asplenia is discussed. There is a statistically significant linkage between the cono-truncus and the A—V region in the present material. All cases with A—V anomalies have malformed cono-truncus regions. All cases with cono-truncus anomalies and adequate description of the A—V regions have malformations of the latter. Two cases with normal cono-truncus have normal A—V regions.

The interrelationship between the cono-truncus and the A—V region is dis-

cussed. There is an unusually high incidence (97 per cent) of abnormal A-V region in linkage with an abnormal cono-truncus region. There is evidence that the A-V canal cushions fuse before the septation of the cono-truncus is complete. This fusion occurs when the spleen is in its early formative stage, in Horizon XVI. The spleen is congenitally absent in all cases. In view of these facts it is concluded that the abnormal A-V region in the cases presented might have been primary to the coexistent cono-truncus anomalies.

Clinically, cases of Type B may mimic an uncomplicated Tetralogy of Fallot. Attempts at surgical anastomoses failed in four cases in this category. This was presumably due to the severe associated defects, and to the pulmonary arteries' being hypoplastic. Minor surgical procedures have caused death in three instances: one after incision of an atretic anus, another after adenoidectomy, and a third after tonsillectomy. Most of the cases fall within the age range of birth to 1 year. Roentgenologic examination of the abdomen to establish the position of the stomach, the shape of the liver and a possible asplenia should aid in the diagnosis of this syndrome.

The etiology of asplenia, a teratologic syndrome of visceral symmetry, has not been discussed. The cases presented do not furnish data for such a discussion.

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Addendum

While this paper was in press *Smyth's* (1955) report on "lateroposition of the atrial appendages" was published. *Smyth* has compiled data on 18 cases of this anomaly, including the four instances mentioned on p. 91. In all 18 cases there was transposition of the great arteries. Thirteen cases had anomalous A—V regions, and four had normal A—V ostia (*Birmingham*, 1892/93; *Ngai*, 1935; *Harris & Farber*, case 12, 1939; *Dixon*, case 2, 1954), as inferred from the original case reports. Most commonly there was tricuspid atresia or stenosis.

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Ventricular appendages

Right aortic arch

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TABLE A¹
The spleen with persistent truncus arteriosus

was present; the symbol, —, indicates that the feature was reported absent; and a blank space

Type A. Cases of agenesis

	Age	Sex	Levocardia	Dextrocardia	Interatrial septal defect	Foramen ovale	Persistent ostium primum	Interventricular septal defect	Cor triatrium
Krausse, # 2, 1905	9 d	M	+	+			+	+	+
Garvin, 1927	?	?	+	+			+	+	+
Kimura, 1930	3 w	M		+	+		+	+	
Shapiro, 1930	14 m	M	+	+			+	+	-
Gasser <i>et al.</i> , # 1, 1952	11 w	F		+	+		+	+	+
Baumann, # 1, 1954	3 d	M	+	+			+	+	+
Author, # 1	Sb	M	+	+			+	+	+
» # 2	3 d	M	+				+	+	
» # 3	4 w	F	+				+	+	
» # 10	5 m	M	+	+			+		

¹ In this and the following three tables: the symbol, +, indicates that the feature was present; the symbol, -, indicates that this feature was not mentioned in the case report.

nesis

Interventricular septal defect
Cor bilobum

at the

TABLE B

TABLE B

Spleen with pulmonary atresia or stenosis

		Right aortic arch		Systemic veins		Anomalous connection, partial		Anomalous connection, total		Left sup. vena cava		Right sup. vena cava		Inferior vena cava		Coronary sinus		Pulmonary veins		Anomalous connection, partial		Anomalous connection, total		Common pulmonary vein		Lungs, abnormal lobation		Lungs, abnormal lobation, symmetric		Stomach transposed		Liver transposed		Liver symmetric		Common mesentery		Remarks	
+	+	+	LA	RA	LA	—	LA	LA	RA	PV	+	+	+	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	Spina bifida.							
+	+	+	LA	RA	LA	—	LA	LA	RA	RA	RS	+	+	+	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	Inv. of atria.							
+	+	+	LA	RA	LA	LA	RA	LA	RS + LSVC	VC	+	+	+	4	4	4	4	4	4	4	4	4	4	4	4	4	4	4	4	4	4	Hep. v. to LA.							
+	+	+	LA	RA	RA	RA	RA	LA	PV	+	+	+	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	“Anom. v. portae”.						
+	+	+	LA	RA	RA	RA	RA	RA	RA	RS	+	+	+	4	4	4	4	4	4	4	4	4	4	4	4	4	4	4	4	4	4	Double azygos v.							
+	+	+	LA	RA	RA	RA	RA	LA	PV	+	+	+	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	Endocarditis.						
+	+	+	(?)LA	?	LA	LA	LA	LA	PV	+	+	+	4	4	4	4	4	4	4	4	4	4	4	4	4	4	4	4	4	4	4	Chinese.							
+	+	+	LA	RA	LA	LA	LA	LA	RA	LS	+	+	+	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	(?) = states LV.							
+	+	+	LA	RA	RA	RA	RA	RA	RA	VC	+	+	+	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	LPV to LA.							
+	+	+	LA	RA	RA	RA	RA	RA	RA	RS	+	+	+	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	Spina bifida.							
+	+	+	RA	RA	RA	RA	RA	RA	PV	+	+	+	4	4	4	4	4	4	4	4	4	4	4	4	4	4	4	4	4	4	4	Hep. v. to RA.							
+	+	+	(?)LA	?	LA	LA	LA	LA	RA	L	+	+	+	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	Hep. v. to RA; Negro.							
+	+	+	LA	RA	LA	LA	LA	LA	RA	Inn	+	+	+	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	Partially pers. LSVC.							
+	+	+	RA	LA	LA	LA	LA	LA	PV	+	+	+	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	Ulcerative tracheitis.							
+	+	+	RA	RA	RA	RA	RA	RA	RA	RS	+	+	+	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	Meningitis.							
+	+	RA	RA	RA	RA	RA	RA	RA	RA	VC	+	+	+	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3								
+	+	RA	RA	RA	RA	RA	RA	RA	RA	RS	+	+	+	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3								
+	+	RA	RA	RA	RA	RA	RA	RA	RA	VC	+	+	+	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3								
+	+	RA	RA	RA	RA	RA	RA	RA	RA	RA	+	+	+	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3								
+	+	RA	RA	RA	RA	RA	RA	RA	RA	az	+	+	+	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3								
+	+	RA	RA	RA	RA	RA	RA	RA	RA	RS	+	+	+	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3								
+	+	RA	RA	RA	RA	RA	RA	RA	RA	VC	+	+	+	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3								
+	+	RA	RA	RA	RA	RA	RA	RA	RA	RA	+	+	+	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3								

?Inv. of atria.

TABLE

Type C. Cases of agenesis of the spleen with transposition of the great arteries

	Age		Dextrocardia	Interatrial septal defect	Foramen ovale	Persistent ostium primum	Interventricular septal defect	Cor bilobata	Transposition of the great arteries	Patient ductus arteriosus	Right aortic arch
		Sex	Levocardia								
Martin, 1826	6 w	?	+	+				+	+	+	+
Epstein, 1886	5 w	F	+					+	+	+	
Kundrat, 1888	4 w	F		+				+	+	+	
Lawrence <i>et al.</i> , 1901	14 w	F	+	+	+	+	+	+	+	+	
Mönckeberg, 1915	4½ m	M		+	+	+		+	+	+	
Pernkopf, # 4, 1926	NB	?	+	+	+			+	+	+	
> # 5, 1926	6 m	M		+				+	+	+	
Fueter, 1938	1 d	M	+	+				+	+	+	
Taussig, 1939	2 m	M		+				+	+	+	
Durie <i>et al.</i> , # 2, 1942	1 m	M	+		+	+	+	+	+	+	
Jaccard, # 1, 1951	10 w	F		+				+	+	+	
Author, # 5	2 m	F	+	+				+	+	+	
> # 8	4 m	F	+	+				+	+	+	
> # 11	6 m	M	+	+				+	+	+	

TABLE

Type D. Cases of agenesis of the spleen without transposition of the great arteries

Valleix, 1834	8 d	M	+	+		+		?
Birch-Hirschfeld, 1871	NB	M		+				
Bossert <i>et al.</i> , 1920	9 m	?		+		+	+	
McLean <i>et al.</i> , 1922	3 m	M	+	+				

TABLE C
Disposition of the great arteries, without pulmonary atresia or stenosis

Transposition of the great arteries										Remarks
Patent ductus arteriosus					Right aortic arch					
Anomalous connection, partial					Anomalous connection, total					Systemic veins
+ + + + +	+ + + + +	+ + + + +	+ + + + +	+ + + + +	Left sup. vena cava	Right sup. vena cava	Inferior vena cava	Coronary sinus	Pulmonary veins	
+ + + + +	+ + + + +	+ + + + +	+ + + + +	+ + + + +	LA RA RA	RA RA	RA RA	—	Anomalous connection, partial	Anomalous connection, total
+ + + + +	+ + + + +	+ + + + +	+ + + + +	+ + + + +	LA RA LA	RA —	RA —	—	Common pulmonary vein	
+ + + + +	+ + + + +	+ + + + +	+ + + + +	+ + + + +	LA RA LA	LA —	LA —	—	Lungs, abnormal lobation	Lungs, abnormal lobation, symmetric
+ + + + +	+ + + + +	+ + + + +	+ + + + +	+ + + + +	LA RA LA	LA —	LA —	—	Lungs, abnormal lobation	
+ + + + +	+ + + + +	+ + + + +	+ + + + +	+ + + + +	LA — RA	— RA	— RA	—	Stomach transposed	Coarc.
+ + + + +	+ + + + +	+ + + + +	+ + + + +	+ + + + +	+ + + + +	+ + + + +	+ + + + +	—	Liver transposed	
+ + + + +	+ + + + +	+ + + + +	+ + + + +	+ + + + +	+ + + + +	+ + + + +	+ + + + +	—	Liver symmetric	Hep.v.to RA.
+ + + + +	+ + + + +	+ + + + +	+ + + + +	+ + + + +	+ + + + +	+ + + + +	+ + + + +	—	Common mesentery	
+ + + + +	+ + + + +	+ + + + +	+ + + + +	+ + + + +	RS VC	RS VC	RS VC	—	Common pulmonary vein	Hep.v.to LA.
+ + + + +	+ + + + +	+ + + + +	+ + + + +	+ + + + +	RA +	RA +	RA +	—	Lungs, abnormal lobation	
+ + + + +	+ + + + +	+ + + + +	+ + + + +	+ + + + +	+ + + + +	+ + + + +	+ + + + +	—	Stomach transposed	Coarc.
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+ + + + +	+ + + + +	+ + + + +	+ + + + +	+ + + + +	+ + + + +	+ + + + +	+ + + + +	—	Liver symmetric	Inv. of atria.
+ + + + +	+ + + + +	+ + + + +	+ + + + +	+ + + + +	+ + + + +	+ + + + +	+ + + + +	—	Common mesentery	
+ + + + +	+ + + + +	+ + + + +	+ + + + +	+ + + + +	PV +	—	—	—	Common pulmonary vein	Hep.v.to RA.
+ + + + +	+ + + + +	+ + + + +	+ + + + +	+ + + + +	L Inn (+) +	—	—	—	Lungs, abnormal lobation	
+ + + + +	+ + + + +	+ + + + +	+ + + + +	+ + + + +	R Inn +	—	—	—	Stomach transposed	Coarc.
+ + + + +	+ + + + +	+ + + + +	+ + + + +	+ + + + +	—	—	—	—	Liver transposed	
+ + + + +	+ + + + +	+ + + + +	+ + + + +	+ + + + +	—	—	—	—	Liver symmetric	Hep.v.to LA.
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IMPLICATIONS OF AGENESIS OF THE SPLEEN ON THE PATHOGENESIS OF CONO-TRUNCUS ANOMALIES IN CHILDHOOD

An Analysis of the Heart Malformations in the Splenic
Agenesis Syndrome, with Fourteen New Cases

By

BJÖRN L. IVEMARK

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